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Ca

Bulletin of

Cancer Progress

no hopeless patients . . . only physicians without hope

In the treatment of *advanced* breast cancer the probability that we may ultimately fail in our efforts must not deter us from providing the best possible program of palliative therapy.

Cancer of the breast is a malign and monstrously destructive disease which has the sinister distinction of being the commonest single site of cancer in the human body. Current statistics indicate that in the United States one woman in twenty (representing 5 per cent of the female population) is destined to develop breast cancer and the risk of this probability increases steadily with age.

Despite the very best of treatment by the most skillful of surgeons, the five-year survival rate for operable breast cancer is only 50 per cent. This is true the world over. Thus, an appalling number of patients with advanced, metastatic or inoperable breast cancer will seek medical aid in their terminal affliction. This grave problem presents a challenging responsibility of major magnitude to the medical profession in the total care of breast cancer. For it is in the palliative treatment of this advanced disease that physicians and surgeons alike can distinguish themselves by their deftness and devotion to duty.

A carefully considered regimen of palliative therapy offers the patient a great deal of comfort and often prolongation of life. Radiotherapy is of great benefit to patients with localized recurrences or skeletal metastases. Radioactive colloidal gold is particularly valuable in patients with pleural effusion or ascites, and radioactive phosphorus has been recommended in bone lesions.

In the presence of disseminated metastatic disease the sex hormones with androgenic or estrogenic activity will produce a favorable objective response in 20 to 30 per cent of the patients. These remissions will be time-limited and the sex steroids must be carefully selected with regard to the "menopausal age" of the patient. Corticoids have also proved to be effective in the palliative treatment of advanced breast cancer. Many other chemotherapeutic agents have been used but with more limited success.

Endocrine ablation procedures such as oophorectomy, adrenalectomy and hypophysectomy are ever-increasingly important adjuncts in the sequence of therapy in patients with advanced breast cancer.

Thus, there *is a great deal* that can be done for patients with advanced breast cancer. This is by no means a hopeless condition—"there are only those who have become hopeless about it."

Edward F. Lewison

Cover — *Portrait of the Artist's Wife and Child* by Ivan Meštrović (1883-). Bronze, life-size, 1924. Czechoslovak Modern Gallery, Prague. From *Schmeckebier, L.: Ivan Meštrović, Sculptor and Patriot. Syracuse, New York, Syracuse University Press, 1959: plate 37.*

Fifty years ago, Rodin characterized the young Ivan Meštrović as "the greatest phenomenon among the sculptors." A survey of the sculptor's life and work to commemorate his seventy-fifth year demonstrates not only the continued vitality and extraordinary stature of this artistic phenomenon but, also the persistence of certain basic ideas of individual freedom and the rights of men which have made him both a political and artistic personality of significance.

Breast cancer is relatively more common in single than in married women, in women without children and in mothers with a history of abnormal lactation . . . the common denominator may be the failure of physiologic function. *Lewison, E. F.: Breast Cancer. Baltimore. The Williams & Wilkins Co. 1955; p. 105.*

NEWSLETTER

SEPTEMBER-OCTOBER, 1959

Kaplan (Stanford University School of Medicine) reduced the incidence of lymphoma in mice exposed to leukemogenic doses of whole body X radiation with single doses of hydrocortisone. No effect was observed with 0.3 mg. dose levels of hydrocortisone, but at 1.0 mg. dose the lymphoma incidence was reduced from 85 per cent in controls to approximately 50 per cent. The 3.0 mg. dose suppressed lymphoma incidence to 22 per cent.

Thiery and others (State University, Ghent): Virus-like particles have apparently not been found before in chemically induced tumors. Now, however, intra- and extracellular particles indistinguishable from virus-like particles have been seen in ultra thin sections of chemically induced uterine cervical carcinoma examined in the electron microscope. No such particles were discovered in liver, spleen, intestine, colon, breast or pancreas of the treated mice. The uterine carcinoma was induced in C3H/A mice with biweekly applications of 3,4-benzpyrene. It cannot be proved, of course, that the particles described are not simply due to viral infection, but it is difficult to explain why contamination should remain confined to the cervix.

Lombard and Witte (Philadelphia) report that birds and mammals living in a zoological garden are, like man, living longer and getting cancer more frequently. Postmortem records of the Philadelphia Zoological Garden are continuous since 1901. From that date to 1931, the frequency and types of malignant tumors in mammals and birds did not change. In 1935, traditional and often inadequate diets were replaced by controlled diets and since then, the frequency of tumors has increased in animals of a number of taxonomic groups. In the opinion of these scientists, some but not all of the increase can be attributed to greater longevity. Other agents must be considered, such as the increased distribution of carcinogens in the environment and diet of the animals. Among the primates, the genitourinary and accessory digestive organs, such as the liver, biliary system and pancreas, and endocrine organs were most

frequently involved. In the carnivores, the organs most frequently involved were those of the endocrine glands and respiratory system, and in birds, the genitourinary system, the digestive organs, and the lungs were frequent sites of neoplastic change.

Green and Corso (Bronx Veterans Administration Hospital) performed skin homografts on seven patients with lymphomas, three patients with miscellaneous conditions affecting their reticuloendothelial systems and four control patients. The ability to reject skin homografts was taken as a measure of immunological "health." Impaired ability to reject the grafts was observed in most of the patients with lymphomas, in a patient with bronchogenic carcinoma, and in a patient with multiple myeloma. The immunologic handicap of cancer patients is of interest if marrow homotransplants become a form of therapy in patients with lymphomas.

Burdette (University of Utah College of Medicine) reports that ecdysone (see CA: 7:144, 1957; 9:viii, 1959), the hormone secreted in the brain of insects which causes regression of larval tissues, has been isolated and crystallized. Preliminary tests indicate that it is a steroid-like compound. Mice inoculated with either the Gardner tumor or Sarcoma 180, receiving ecdysone, showed tumor regression in some cases.

Pentimalli (Rome): Homogenates of normal tissues and urine incubated with rat cancers completely destroy the transplantability of the tumors. Homogenates of muscle, lung and spleen cytolysed tumor cells without affecting normal cells; brain, embryonal tissue and blood were inactive, and so were whole cells of all tissues tested. The active principle is cell-bound, strongest in the supernatant and destroyed either by boiling or adding of blood. The material is toxic when given intravenously.

Zilber (Moscow): Azo dye binds to liver protein, becomes antigenic and the antigenic complex disappears. At the same time, a tumor antigen appears in the liver tissue, and it can be adsorbed onto normal erythrocytes and detected; but it escapes detection by Schultz-Dale technique in liver tumors. With actively acquired tolerance, it is now possible to differentiate between normal liver and hepatoma antigens.

Kidd (New York): Antilymphoma immune rabbit sera act powerfully and to some extent selectively against a va-

(Continued after Page 180)

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TOPIC: BREAST CANCER

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Keeping up

Cancer Operations that End Badly

The effort and expense involved in surgical treatment of cancer is sometimes not justified on the basis of the results. What has been undertaken in the hope of bringing relief from pain and suffering or sometimes in the hope of cure may bring only disappointment. This may be because the surgeon goes too far or does too much or because the tumor grows and spreads in spite of treatment or perhaps because of it. Sometimes the surgeon persists because he believes that "something has to be done" or because he has faith in his ability and the "benefits" of surgery. Occasionally he may rationalize: without surgical treatment the patient will die; therefore, he has "nothing to lose" and "deserves a chance." Often when the operation fails the patient loses all and the surgeon loses nothing. The author recommends consideration of these general factors bearing on the management of a specific case: (1) Weigh carefully the patient's condition and assess his ability to recover from the proposed treatment. (2) Review the natural history of the disease —its possible and probable extent, curability with radical treatment, effectiveness of palliative operation and survival with nonoperative treatment. (3) Consider carefully the magnitude of the operative procedure—tissue removal, stress, blood loss, physiologic and anatomic deficits and immediate and late risks of complications and death. (4) Assess the experience, judgment and proved ability of the surgeon, the anesthetist and other participants. Harm to the patient is most likely to result from surgical inexperience and poor judgment. Extensive operations must be undertaken with great care. They are recommended only when there is reasonable hope that the lesion can be encompassed, that the patient can withstand the procedure and that the benefits will be significantly better than those from a less radical operation. Cordotomy in metastatic cancer, adrenalectomy or hypophysectomy for advanced breast cancer, hemipelvectomy for metastatic tumor, pelvic viscerectomy for spreading cervical cancer are likely to turn out badly and are rarely indicated. Palliative procedures are not always the answer and should not be undertaken indiscriminately. Operations become less important as cancer advances. The surgeon should avoid those operations which are most likely to bring no benefit to his patient and which tend to end badly.

Gius, J. A.: Cancer and cacotelic [kakos, Gr., bad: telikos, Gr., ending.] operations. Surg., Gynec. & Obst. 108:743-744, June, 1959.

Penn Cancer Test

The author reports one of several studies made upon invitation of the originators of the Penn-Hall seroflocculation test for cancer. The antigen used was supplied by Hall and the methods were learned and practiced in the laboratories of Hall and Penn. The test was applied to 241 cancerous and 1608 noncancerous hospital patients and to 129 normal ambulatory individuals. Of these normal individuals, 5 per cent were positive; of the noncancerous patients, 19 per cent were positive; and of the cancerous patients 43 per cent were positive to the test. It is,

with Cancer

therefore, highly improbable that the test is cancer specific. This is in agreement with four additional similar studies.

Hill, J. H.: The Penn seroflocculation reaction in cancer diagnosis. Proc. Soc. Exper. Biol. & Med. 97:524-527, March, 1958.

Leukemia Incidence

The marked recorded increase in the incidence of leukemia and lymphomas in the past 30 years is attributed to (1) the continuing increase of man-made additions to the natural environmental background of ionizing radiation, (2) the increased use of marrow-depressing drugs, and (3) the growing contamination of the atmosphere with leukemogenic chemical pollutants. The relative importance of these several factors cannot be determined accurately. All three, as well as other factors associated with the changing standard of living, deserve further investigation.

Schwartz, E. E., and Upton, A. C.: Factors influencing the incidence of leukemia: special consideration of the role of ionizing radiation. Blood 13:845-864, Sept., 1958.

Conservatism in Cancer Operations

There are similarities in the clinical behavior of different types of cancer, but it is not correct to think of cancer as a single disease entity, nor to assume that "principles" of cancer surgery are applicable to the treatment of all types of cancer. Observations of cancer cells in the blood of patients with operable cancers suggest that systemic dissemination depends less on the time or the type of operation than upon the resistance of the host and the ability of metastases to implant and grow. In this concept lies an explanation of the fact that earlier and more extensive operations have failed to reduce the systemic spread or to alter the death rate. There are at least three biologic types of cancer: (1) cancers that do not tend to metastasize, (2) those that metastasize chiefly to the regional lymph nodes and (3) those that metastasize systemically, even before the primary tumor is recognized. Radical operations are not necessary in the localized group and do not cure patients with cancers that have already spread through the blood. It is only in treatment of the cancers that tend to metastasize solely to regional lymph nodes that radical resections of lymph nodes are of value. In some cancers, such as squamous cell cancers of the mouth, metastasis limited to regional lymph nodes is so common that radical operations are well justified. Other cancers, such as those of the lung, tend to be so widely disseminated before the primary tumor is recognized that little is gained by extending the scope of the operation. Here, involvement of lymph nodes is more a sign of incurability than an indication for radical operation. Finally, many cancers, such as those in polyps of the rectum, tend to be localized and can be cured by local treatment. If extensive operations are done to cure localized tumors, the morbidity and mortality far exceed the possible dangers of recurrence after local treatment. Treatment must be individualized according to the biologic type of cancer.

Crile, G., Jr.: The case for conservatism in operations for cancer. S. Clin. North America 38:1215-1220, Oct., 1958.

at a glance . . .

one-minute abstracts of the literature on breast cancer . . .

Development of Breast Cancer Surgery

This short history of the development of surgery for breast cancer recounts the major contributions since recognition of the disease by the Egyptians in 1500 B.C. Up through the 17th century, crude surgical methods brought high mortality and morbidity. During the 18th century, theories on the origin of cancer emphasized its local nature and only tumorous tissue was excised. In 1801, Joseph Adams of the Royal College of Physicians, advocated wider excision of tissue. In 1867, Charles Moore of the Middlesex Hospital (London) emphasized *en masse* removal which is basic to modern cancer surgery. Lord Lister, in the 1860's, recommended complete dissection of the axillary lymph nodes and fat, a procedure also stressed by W. Mitchell Banks, surgeon to the Liverpool Royal Infirmary. Basic investigations of the mode of spread of cancer carried out by such men as Volkmann, Heidenhain, Stiles and Velpeau indicated that lymphatics carried the disease into pectoral fascia and pointed up the need for its removal. In America these ideas were promulgated by S. W. Gross at Jefferson Hospital in Philadelphia. Volkmann in 1875, first advocated excision of pectoral muscles when there was gross involvement with tumor, and W. W. Cheyne extended this idea by removing portions of the pectoralis major in all cases. W. S. Halsted combined all previous ideas and in 1891 published his procedure to which little has been added since. Willy Meyer, in 1894, independently described a similar procedure. In 1905, W. S. Handley advocated wide removal of subcutaneous tissue and fascia. Since the turn of the century the radical mastectomy as done by Halsted has become firmly established as the operation of choice for breast cancer.

Goldenberg, I. S.: The development of surgery for cancer of the breast. Connecticut Med. 23:77-79, Feb., 1959.

Breast Cancer at Johns Hopkins

Five per cent of the female population will develop cancer of the breast, which is the most frequent specific primary site of cancer in either sex. The breast cancer death rate in the United States, between 1930 and 1955, varied only between 21.5 to 23.1. The over-all five-year survival rate in 259 female patients with breast cancer at Johns Hopkins Hospital between 1941 and 1945 inclusive was 36.7 per cent and the 10 year rate was 23.2. Of these 259 patients 185 (71 per cent) were treated by radical mastectomy. Of these, 46 per cent survived five years—71 per cent for those with localized disease and 34 per

cent for those with regional metastases. Simple mastectomy in 17 per cent of the group yielded a five-year survival rate of 23 per cent. Postoperative radiotherapy did not improve the results. The uniformity of survival rates from various modes of therapy—simple mastectomy, local excision, radical mastectomy, modified radical mastectomy, each with and without x-ray and radium therapy and radiotherapy alone—may be explained by host-tumor relationships. Immunological processes have a role in the prognosis of breast cancer. Radical mastectomy meticulously performed at the earliest possible time gives the best chance of cure. Approximately 32 per cent of breast cancers are localized when first diagnosed. The hematogenous spread of free cancer cells in breast cancer is far from uncommon. No generalizations can be made concerning the treatment of cancer of the breast; each patient should be considered as an individual problem and treated accordingly.

Lewison, E. F.: The results of treatment of breast cancer at the Johns Hopkins Hospital 1941-1945 with a discussion. [Collective review.] Internat. Abstr. Surg. 107:313-329, Oct., 1958.

Cancerous vs. Normal Tissues

Using the ultraviolet microscope and a globulin-fluorescein complex stain, the fluorescence characteristics of normal and breast tumor tissues were compared. Clear distinctions were made between normal and malignant cells. Normal tissue cells take the special stain well and can be demonstrated by fluorescence in ultraviolet light. Cells in malignant tumors do not stain well and cannot be demonstrated by fluorescence. Hyperplastic tissues and those from fibroadenomas of the breast show the fluorescent characteristics of normal tissue and are thus easily and clearly distinguishable from neoplastic tissue. The author suggests the possible application of this technique to identification of true precancerous conditions in some cases of gross hyperplasia. Ordinarily the diagnosis of conditions by frozen sections using ordinary stains presents difficulties in the very type of case in which most help is required. The distinction between a neoplasm and normal or hyperplastic tissue is clear cut and definite by this method of fluorescence microscopy. This technique has possibilities in diagnosis of malignant changes in sites other than the breast.

Louis, C. J.: Tumours of the breast, a study employing a histochemical technique. Brit. J. Surg. 46:147-155, Sept., 1958.

Treatment of Breast Cancer

There is today no satisfactory set of principles governing the treatment of carcinoma of the breast. The surgeon must still use his judgment in each individual case. If a patient is going to die of breast cancer she will, in all probability, do so within five years after operation. If she does not die, either we have succeeded in extirpating the malignant cells by a Halsted operation, we have arrested them in the lymph nodes and perhaps destroyed them by irradiation (McWhirter), the patient's own tissue composition has altered so that a predisposition to cancer formation no longer exists (Macdonald) or, finally, the tumor was not malignant to start with. These authors analyze statistically 358 private patients with breast cancer between 1925 and 1954 in Atlanta, Georgia. Among patients who have not borne children breast cancer appears later in life and progresses more slowly than in patients who have been mothers. With proper selection of individual cases simple mastectomy seems to be as good as radical mastectomy.

Skandalakis, J. E.; Gray, S. W.; Macris, A.; Mitchell, W. E.; Nicolson, W. P., Jr., and McRae, F. W.: Carcinoma of the breast. Surgery 45:912-929, June, 1959.

Breast Cancer

In women the three most common sites of cancer are breast, uterine cervix and skin. Breast cancer is more than twice as frequent as cancer of either the cervix or skin. The incidence curve of breast cancer in the United States steadily goes up. Modesty and embarrassment at examination are important factors in delaying diagnosis

of the breast. The average woman would prefer pelvic examination, under proper conditions of draping, to a breast examination. The physician also is to blame for some of the delay in diagnosis. He not infrequently sees physiologic breast lumps —premenstrual areas of mastitis, adenosis and hyperplasia—disappear spontaneously. He hopes that this particular lump may also disappear and he is apt to "take a chance." In 1920 only 22.6 per cent of breast cancers at Memorial Hospital (New York) were operable. Without a change of criteria of operability that figure is now 80.3 per cent. Among the improvements in therapy are high voltage x-ray radiation, application of hormones, ovariectomy, adrenalectomy, hypophysectomy and super-radical mastectomy. Extension of conventional radical mastectomy to include the internal mammary chain requires the talent of a surgeon experienced in this field, when low operative mortality can be maintained. Due in large part to educational activities of the American Cancer Society women with breast cancer are coming earlier to their physicians. A little better than half of primary operable cases are cured. When cancer is confined to the breast alone the five-year salvage rate is 77.5 per cent and the ten-year rate 53.8 per cent. When the axilla is involved these figures are 39.4 and 21.2 respectively. These results are far from satisfactory and newer approaches other than surgery, irradiation and hormones are urgently needed. Oophorectomy should be performed in case of metastasis or local recurrence. For osseous metastasis testosterone is the treatment of choice. It may be given as a depot injection or in the form of one of the newer compounds like prednisone. Cortisone has been reported to be of similar value. From oophorectomy approximately 40 per cent improvement may be expected in breast cancer in young women with advanced metastatic disease. This procedure is not recommended for elderly women. Objective response followed adrenalectomy in 42.5 per cent of 300 cases. Objective response, particularly in the bones and lungs, followed hypophysectomy in approximately 50 per cent of 300 cases. We are still in a stage of development of knowledge concerning therapy of breast cancer. More time will be required to determine the best form of therapy for each case.

Adair, F. E.: A discussion of breast cancer. New York J. Med. 59:2149-2153, June 1, 1959.

Androgen-Antimitotic Breast Cancer Therapy

No spectacular improvement can be expected from existing methods of treatment of breast cancer based upon the assumption that the disease in the early stages is localized to the breast and adjacent lymph nodes. At present the prognosis is largely one of conjecture. A woman under 30 is almost certainly doomed within a year, especially if the breast cancer arises in association with pregnancy or lactation. In a woman of 65 or more prognosis is relatively favorable, but between these ages the outlook is completely uncertain except in the known advanced case. Even with such radical measures as oophorectomy, adrenalectomy and hypophysectomy worthwhile palliative results are obtained in only 50 per cent of cases, and good remissions lasting for a year or more occur in less than 25 per cent. Similar remissions may be obtained with androgen therapy especially when the symptoms are from bony metastases. It occurred to the authors to use, in endocrine-resistant cancers of the breast, an antimitotic drug in conjunction with androgen therapy. The alkylating agents have been used successfully in the reticuloses but surprisingly few attempts have been made to use these agents in treatment of solid cancers. In this series testosterone with oophorectomy constituted the endocrine part of the therapy and triethylenethiophosphoramide (thioTEPA) was chosen as the alkylating agent. Testosterone and this antimitotic both inhibit cancer growth but by different methods and therefore can be expected to give a higher percentage of favorable results. The intramuscular route of administration was used. Regression of tumor growth was attained in eight out of

the 11 patients treated with thioTEPA alone and in 22 out of 23 patients receiving thioTEPA and testosterone. Those patients showing regression of the tumor experienced marked subjective improvement in their sense of well-being. The depressive action of thioTEPA on the bone marrow was the most serious complication encountered. Objective improvement was obtained in 88 per cent of 30 cases whereas tumor regression may be expected in only 33 per cent of breast cancers treated with testosterone alone. ThioTEPA alone in a series of 10 cases gave tumor regression in three cases. The increased effect of the two drugs may be due to synergistic action or more probably to the much greater total dose of thioTEPA that can be used in patients receiving testosterone before marrow depression occurred. The authors suggest the possibility of synthesizing an ethyleneimino compound of testosterone as a single drug giving these combined effects. The clinical, histological and radiological evidence of destruction of malignant cells obtained in the advanced cancers of this series suggest the possibility of completely eradicating a tumor and its metastases by chemotherapy. The authors have abandoned radiotherapy in favor of chemotherapy as an essential part of the primary treatment of early breast cancer. Periodic maintenance doses of thioTEPA were administered following intensive combined therapy. It may be necessary in the future to use other antimitotic agents. Undoubtedly, better agents will be found and better techniques will be devised. The wider use of chemotherapy as an alternative to radiation should be made in breast cancer.

Watson, G. W., and Turner, R. L.: Breast cancer: a new approach to therapy. Brit. M. J. 1:1315-1320, May 23, 1959.

Survival in Breast Cancer

A study of patients with early and with advanced breast cancer at the Royal Marsden Hospital (London) is reported. Data are tabulated in 19 figures and seven tables relating to: trends in breast cancer mortality; trends in treatment results; short survival in early cases with respect to grade and size of the tumor, length of the history, site of the tumor and age of the patient; analysis of Stage 1 patients dying within two years of treatment; long survival in advanced cases with respect to grade, size, site, length of history of the tumor, age and menopause; analysis of Stage 4 patients living more than three years after treatment. The author concludes that failure in early cases is usually due to distant blood-borne metastases. Mastectomy is considered the method of choice in early cases, for diagnosis and grading as well as for treatment of well localized disease. The extent of mastectomy depends on the individual case; points favoring a bad prognosis should limit the use of surgery. Large medial tumors with a short history are the only ones where irradiation before mastectomy is often indicated in Stage 1. Patients with inner half tumors and those with outer half tumors having histologic involvement of axillary lymph nodes should have postoperative irradiation. Artificial menopause should be considered as part of the treatment in young women before the menopause who have Grade III tumors with multicentric origin and extensive lymphatic permeation or involvement of axillary fat. In late cases success may be achieved in the premenopausal group if menopause is induced and irradiation employed. In the elderly, estrogen treatment combined with irradiation may give long-term survival. Adrenalectomy, hypophysectomy and radioactive pituitary implants must be assessed in the light of what may be achieved with less drastic measures.

Smithers, D. W.: Cancer of the breast; study of short survival in early cases and of long survival in advanced cases. Am. J. Roentgenol. 80:740-758, Nov., 1958.

Prophylactic Castration in Breast Cancer

Although castration has been accepted as a palliative measure in the treatment of advanced breast cancer, the suppression of ovarian function, by either surgery or irradiation as a prophylactic

method before metastases occur, has been a controversial problem. The authors report observations on 200 patients less than the age of 50 years who had undergone radical mastectomy for cancer of the breast and at operation had no clinical manifestation of metastatic spread beyond the axillary lymph nodes, although there was no proof that they had no distant metastases. All patients were referred to the Tumor Clinic of the Michael Reese Hospital (Chicago) between Jan. 1, 1942 and Dec. 31, 1951, and were followed for at least five years. Seventy-eight patients underwent prophylactic castration, either by bilateral oophorectomy or irradiation of the ovaries, shortly after radical mastectomy. Fifty-nine per cent of these survived more than five years, as compared with 3.6 per cent of the 122 patients who were not castrated. The castration effect was particularly favorable in the age group over 40 years where a survival rate of 6.8 per cent seems to indicate that castration may be of importance during early menopause. Among 66 women who died within five years after mastectomy, survival of the castrates was longer than that of the women who had functioning ovaries. The authors believe that these observations provide sufficient justification for advocating prophylactic castration in all women with carcinoma of the breast who are still menstruating regularly or otherwise show signs of ovarian activity.

Rosenberg, M. F., and Uhlmann, E. M.: Prophylactic castration in carcinoma of the breast. A. M. A Arch. Surg. 78:376-379, March, 1959.

Treatment and Diagnosis of Breast Cancer

Consistent evidence has shown that local and regional treatment, however early, fails to control mortality from breast cancer. In the past 30 to 35 years, trends of recorded age-specific mortality from breast cancer are nearly level, despite efforts to control mortality, and are nearly uniform from place to place despite wide differences in these efforts and in the extent of shift to earlier and more extensive treatment. Microscopy fails to reveal dependably the biologic, metastatic or lethal potentialities of many lesions with a cancerous architecture. The inability to differentiate accurately between lethal and nonlethal cancers has allowed the inclusion of nonlethal and very lowly lethal lesions in the treatment of lethal cancers. This inclusion has yielded fictitious increases in survival rates and explains the otherwise inexplicable incongruity between the stability of the recorded mortality on one hand and, on the other the greater use of specialist services and progressively higher survival rates reported from many clinics. It also explains the wide differences among survival rates of different clinics and other inconsistencies in breast cancer data. The literature shows increasing recognition of the limitations of both diagnosis (microscopic) and treatment, but less realization of what is implicit in those limitations. The failure to realize the implications of the limitations is evident in the advocacy of supraradical mastectomy, of self-examination as a means of early detection, and in the continued comparison of survival rates derived from material the comparability of which can not be established even by grading and staging. In Ontario the ratio of the number of patients treated for breast cancer to the number of deaths from breast cancer is 3:1, which ratio is probably attributable to the inclusion of many nonprogressive lesions as lethal cancer.

McKinnon, N. E.: The present status of the treatment and the diagnosis of cancer of the breast. Canad. M. A. J. 78:781-785, May 15, 1958.

Steroid Therapy After Adrenalectomy in Breast Cancer

It is well known that certain tumors are dependent upon endocrine influences and that subjective and objective benefit may be derived from hormone therapy. Varying the endocrine status of patients with advanced mammary cancer has become an important part of their management. The mechanism by which improvement is effected is still not clear. In order to assay the extent of endocrine dependency it is necessary to make actual observations of

growth of the tumor by either direct or indirect means, under steroid therapy. Using a 56-year-old patient who had definite hormonally dependent, advanced breast cancer, as shown by a dramatic improvement after bilateral adrenalectomy, this study was designed to investigate the endocrine physiology of the tumor by subjecting the patient to a detailed metabolic analysis while she received various combinations of hormone therapy. It was found that with high cortisone plus estrogen therapy the soft tissue extension of the tumor showed increased size and vascularity. With high cortisone dosage plus high dosage testosterone therapy and with maintenance cortisone plus high dosage testosterone therapy, the size and vascularity of the tumor were reduced. Urinary calcium excretion at first appeared to offer evidence of recession of metastatic tumor in bone, but further study of phosphorus and nitrogen curves indicated that this was largely a reflection of changes in nitrogen metabolism while the patient was on androgen therapy. This finding provides evidence that calcium and phosphorus metabolic balances studied in such a patient may not reflect solely the changes in growth activity of metastatic foci and bone.

Bloomer, W. E., and Haves, M. A.: The effects of varying steroid therapy on metastatic mammary carcinoma after adrenalectomy. Cancer 11:1011-1024, Sept.-Oct., 1958.

Breast Cancer in Younger Women

An analysis is reported of 549 cases of histologically confirmed breast cancer in patients, 35 years of age or younger, observed at Memorial Center (New York), from 1937 through 1949. All patients have a minimal follow-up period of five years from the date of admission. The extensive data presented in the text are summarized in 22 tables relating to: clinical classification, family history, multiple primary neoplasms, previous gynecologic history, subsequent gynecologic surgery, nipple discharge, pathologic diagnosis, location of tumor and clinical cure rate, age group and clinical cure, location of cancer and incidence of involved axillary nodes, histologic type and clinical cure, clinical cure rate in pregnancy, management of subsequent pregnancy with uninvolved axillary nodes and with involved axillary nodes, incidence of axillary node metastases and clinical cure rates in relation to delay in diagnosis, size of tumor and incidence of metastatic axillary nodes in patients with infiltrating duct carcinoma, tumor size alone related to clinical cure rate in patients with infiltrating duct carcinoma, clinical cure related to size of tumor and metastatic axillary nodes, postoperative x-ray therapy and clinical cure rates, prophylactic castration *vs.* no castration. From their studies the authors suggest that certain stringent criteria of operability which have been given wide attention in the past should be modified. Early diagnosis and prompt radical surgery offer the best chance for survival. Tumors of the breast during pregnancy should be diagnosed and treated immediately. Previous impressions of poor prognosis for breast cancer in the young woman who is not concurrently pregnant must be supplanted by a more hopeful outlook.

Treves, N., and Holleb, A. I.: A report of 549 cases of breast cancer in women 35 years of age or younger. Surg., Gynec. & Obst. 107:271-283, Sept., 1958.

Metastatic Breast Cancer

Although treatment of breast cancer with metastases is discouraging, the conscientious physician can make these patients comfortable enough to enjoy life for considerable periods. Treatment of patients with metastases from breast cancer should be the same whether or not mastectomy has been done. Before starting any treatment a definite diagnosis of metastatic disease must be made by lymph node biopsy, by x-ray of bones and by clinical judgment in the cases of suspected cerebral and hepatic lesions. All treatment of these patients is definitely palliative and not curative. Patients with asymptomatic lesions should not be treated, unless the lesion is in a weight-bearing bone—to prevent pathological fracture. The several therapeutic modalities cannot be properly evaluated unless they are applied one at a time. Lesions of weight-bearing bones are

here again an exception. Some patients improve upon discontinuing therapy with a hormone that has lost its effectiveness. This withdrawal remission should be fully utilized before changing to another form of treatment. Something is always kept in reserve for that time when the disease will be refractory to the currently employed therapy. Only minor differences exist in application of the several therapeutic modalities to the pre- and post-menopausal patient. In the premenopausal patient, irradiation is the best form of therapy whether the lesion is in bone, skin, soft tissue, liver or brain. In case of progression of disease—development of new or advance of old lesions—while radiation is being used, castration, preferably surgical, is the next therapeutic step. Irradiation castration, often incomplete, should be reserved for patients who refuse or cannot tolerate surgical procedure. Castration should not be used as a prophylactic measure but reserved until symptoms appear. If the disease continues to progress after irradiation and castration, androgenic or estrogenic therapy is begun. Testosterone and ethinyl estradiol are the recommended products. About 20 per cent of patients are benefited objectively by androgen therapy, and many more are improved subjectively. Estrogens are used especially in older patients with soft tissue lesions. When hormone therapy becomes ineffective, adrenalectomy or hypophysectomy is indicated. The latter procedure is recently being preferred in spite of the hazard of complicating diabetes insipidus. And finally cortisone, after all else fails, may carry a semiterminal patient in comparative comfort for a considerable period.

Goldenberg, I. S.: A rational program for treatment of metastatic breast cancer. Connecticut Med. 23: 375-378, June, 1959.

Treatment of Breast Cancer

Evidence from Saskatchewan Cancer Services is presented indicating that radical mastectomy followed by radiation gives better results in breast cancer than does simple mastectomy followed by postoperative radiation according to McWhirter's Edinburgh series. In the more advanced stages local surgery, irradiation, hormone therapy, etc., were used in this series as indicated. No one method of treatment can be used in all patients with cancer of the breast. The majority of cases are seen when the disease has apparently spread no further than the axilla, the primary tumor being still mobile. It is conceded that McWhirter's method is properly applicable to some patients in whom the disease is too advanced for radical mastectomy but still localized to the axilla and chest wall. The author's method differs from McWhirter's only in that radical mastectomy is preferred to simple mastectomy whenever possible. McWhirter's contention that, when the disease is confined to the breast, dissection of the axilla is unnecessary is answered by the statement that similarly it may be argued, if the axillary nodes are not involved, radiotherapy in this region is also pointless. Morbidity from radical mastectomy—swelling of the arm and limited motion—is not serious when physiotherapy is commenced immediately after the operation. In McWhirter's series considerable morbidity from postoperative radiotherapy was encountered. The gross five-year survival rate in this Saskatchewan series was 52 per cent compared with 42 per cent in the Edinburgh series.

Watson, T. A.: Treatment of breast cancer; comparison of results of simple mastectomy and radiotherapy with results of radical mastectomy and radiotherapy. Lancet 1:1191-1194, June 6, 1959.

It is a safe practical rule to regard every single lump in the breast as a carcinoma unless it is proved otherwise by biopsy and microscopical examination.

Raven, R. W.: Malignant tumours of the breast. In Raven, R. W., Ed.: Cancer. Vol. 4. London. Butterworth & Co., Ltd. 1958; pp. 224-245; p. 232.

Relationship between Benign and Malignant Breast Disease

Edward F. Lewison, M.D.

The relationship between breast cancer and benign breast disease demands the keenest kind of critical appraisal. The strength of such a study rests upon the weakness of our current differential diagnosis and surgical treatment. Perhaps the significance of chronic cystic mastitis lies in the insignificance with which we so often regard it. I am sure that each of us can recall at least one patient in whom a perfectly benign breast lesion was successfully excised—only to be followed some years later by breast cancer well within the operative area. These striking examples of anatomic relationship seem to be a link that is "a little more than kin, and less than kind." However, one must *not* be beguiled into believing that a relationship exists merely because *post hoc, ergo propter hoc*—after this, therefore because of this. The pitfall of this kind of presumptive reasoning lies within the very shadow of truth.

The term benign breast disease enfolds in its indiscriminate embrace a galaxy of "synonyms" all of which are in common use and many of which describe variations of the same clinical condition. A strange, complex and hybrid glossary such as fibroadenosis, fibrocystic disease, blunt duct adenosis, chronic cystic mastitis, mastopathy, Reclus' disease, sclerosing adenosis, Bloodgood's blue-domed cyst, mazoplasia, Schimmelbusch's disease, mammary dysplasia and others are oft repeated in the literature, thus adding chronicity to confusion.

Although the name "chronic cystic mastitis" is considered objectionable by such distinguished pathologists as Foote and Stewart because "it conveys no indication of the presence or absence of many characteristic histopathologic changes, moreover, it implies a common etiology for a variety of lesions most of which are anything but basically inflammatory processes," yet clinically the name is useful even if not pathologically precise or strictly descriptive. In the United States, at least, chronic cystic mastitis is understood by all, advocated by authority and recommended by custom. For the purpose of simplicity the term chronic cystic mastitis as used in this discussion will include fibroadenoma, cystic disease, adenosis, intraductal hyperplasia and papilloma as the predominant pathologic lesion.

Our own clinical investigation[10] of this problem constituted a long-term follow-up survey of all patients operated upon at the Johns Hopkins Hospital for chronic cystic mastitis between 1925 and 1941 inclusive. During this period there were 451 patients who underwent surgery and 385 —or 85 per cent—were successfully followed over a 1- to 25-year period. The operation performed was predominantly local excision; however, some patients had a simple mastectomy and a few had a radical mastectomy. Over the course of years a total of seven patients—1.8 per cent—out of 385 subsequently developed breast cancer after a follow-up period varying from eight to 18 years. It is of some significance to note that four of these seven patients developed cancer in the contralateral breast. When compared to the "normal" expected incidence of breast cancer in women of a similar age-range and followed over a comparable period, this present group of chronic cystic mastitis patients appeared to develop breast cancer 2.6 to 3.6 times as frequently.

These results are in close accord with parallel studies of Warren in Boston, Clagett at the Mayo Clinic, Stout of the Presbyterian Hospital in New York and Kiaer of Copenhagen. The breast cancer incidence for women with pre-existing benign breast disease was found to be 4.5

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times as great as expected in Warren's series, five times as great in Clagett's series and four times as great in Stout's series. In Kiaer's excellent monograph on this subject he followed 321 patients with histologically proved "fibroadenosis" for an average period of 17 years in one group and 11.7 years in another and found an actual incidence of breast cancer four to five times as high as was to be expected. The similarity of these clinical results reveals a striking and significant uniformity.

However, in the natural history of breast cancer the evidence of relationship to chronic cystic mastitis must be carefully explored in a broad clinical and experimental orbit before reaching a final countdown.

The pioneer experimental studies of Goormaghtigh and Amerlinck revealed cystic changes in the mouse breast after prolonged estrogen stimulation. The classic work of Lacassagne indicated that changes characteristic of chronic cystic mastitis were often precursors to breast cancer which could be produced in mice in response to estrogens. Geschickter noted that estrone administered to rats over a long period produced adenosis and cystic changes in the breast. In a group of carefully conducted experiments Pullinger demonstrated that estrogen could produce distention of ducts and acini without the ancillary action of progesterone or prolactin. Moore, Wattenberg and Rose did serial breast biopsies in men treated with stilbestrol for cancer of the prostate and they all revealed changes characteristic of chronic cystic mastitis. Thus, I think it is safe to say that excessive estrogen stimulation plays an important role in the production of chronic cystic mastitis. Whether this relative hyperestrinism is truly a preponderance of estrogen or a deficiency in estrogen antagonists such as progesterone remains to be determined. Such careful investigators as Womack and Copeland favor the view that an anovulatory menstrual cycle leads to a deficiency of progesterone resulting in a prolonged and unopposed period of estrogen stimulation.

There is, of course, extensive experimental evidence in animals which indicates that the development of breast cancer also requires estrogen stimulation as one of its essential prerequisites. Similarly, there can be scarcely any doubt that estrogens are of equal importance in the development and progress of human breast cancer. Those of us who have the opportunity of observing patients with advanced breast cancer recognize that a large number of these tumors are hormone-stimulated. Palliative management of these patients is designed to alter the endocrine environment by means of castration, estrogens or endocrine ablation procedures.

Clinically, of course, there is much to suggest that chronic cystic mastitis is at least hormone responsive if not dependent as it is frequently found in the premenopausal period when the crescendo of normal endocrine activity is on the wane. It is most common in childless or unmarried women and is often related to menstrual irregularity, infertility and anovulatory menses, as well as to the endocrine imbalance associated with stress and emotional tension. Premenstrual mastodynia, engorgement, sensitivity and swelling are usually aggravated by estrogen administration and may be relieved by androgens or a progestogen. Following the menopause the severity of this symptom complex gradually subsides.

The histopathologic observations of Sommers in a series of women with breast cancer are of special interest and indicate the presence of frequent abnormalities in the endocrine glands, particularly pituitary and ovarian hyperplasia. Sommers states that "so far as morphologic observations permit interpretation, about two-thirds of the 207 women with breast cancer gave evidence of a prolonged estrogen stimulation of the endometrium and breast."

No doubt the best proof of the causal relationship between chronic cystic mastitis and breast cancer would be the simple and direct histologic demonstration that the point of neoplastic departure begins in a nidus of benign breast disease. Foote and Stewart confidently say "that we have seen cancer begin in duct papillomatosis (solitary and multiple), cyst, apoc-

rine and epithelium and blunt duct adenosis." In a careful review of the literature one can find many proponents of the "evolutionary" theory who seem convinced of the mystical transformation of epithelial hyperplasia to neoplasia. Kiaer found morphologic transitions to be particularly common in the more pronounced grades of "fibroadenosis." The transition passed gradually from duct adenosis to duct carcinoma which ultimately became invasive.

However, it must be remembered that the pathologic picture of chronic cystic mastitis is exceptionally common even in "normal" women. In a special study of the breasts of 225 routine autopsy cases where there was no previous history of breast disease, Frantz and her colleagues found the frequency of breast abnormality to be high. The actual incidence of latent chronic cystic mastitis was observed to be 53 per cent. Kiaer found that 33 per cent of clinically "normal" breasts examined at autopsy showed latent changes which were histologically indistinguishable from manifest cases of chronic cystic mastitis. However, in patients with breast cancer these associated cystic changes were twice as common and showed a very marked and pronounced degree of epithelial proliferation.

In an interesting follow-up study performed perhaps by putting the cart before the horse, Foote and Stewart reviewed the records of 1200 patients with operable breast cancer and found a previous history of operation for benign breast disease in 2.5 per cent. A control group of 1200 patients with cancer elsewhere in the body was reviewed and the incidence of benign breast disease was only 1.1 per cent or less than half. The histologic appearance of the chronic cystic mastitis was not correlated with the subsequent development of breast cancer.

However, it seems obvious that an accurate and precise differential diagnosis between benign epithelial hyperplasia and malignant epithelial neoplasia is urgently needed. Whereas, it has been said by that distinguished French novelist Anatole France that "the future is a convenient place for dreams," yet a recent report by Louis (See abstract p. 149.) of the University of Melbourne, holds out the hope that "what will be, is!" He studied breast tumors by a new staining technique and found a clear distinction could be made between normal and malignant cells using his globulin-fluorescein complex stain. Normal epithelial cells stained well (the fluorescence was demonstrated by ultraviolet light) but malignant cells did not stain at all. The author compared epithelial proliferation in several types of chronic cystic mastitis with breast cancer and found the method to be infallible in its accuracy. In 35 cases of breast cancer there was no evidence of fluorescent staining and in 36 cases of benign breast disease all epithelial elements stained well. If confirmed, this unique and significant observation would indicate that the biologic behavior of the benign epithelial cell of chronic cystic mastitis is qualitatively different in its physiochemical affinity from the malignant epithelial cell of carcinoma. The originality of this new development may be the forerunner of many important and exciting discoveries in the field of cancer research.

The natural history of breast cancer is extremely difficult to trace. However, the formidable task of recognizing the earliest stage in neoplasia may be greatly facilitated by fluorescent staining. Malignant change is probably a dynamic process as noted by Foulds "advancing through stages that are qualitatively different." The decisive steps in this process are the result of progression, which can be best defined as an irreversible qualitative change in the character of the individual cell. Although chronic cystic mastitis may progress in many diverse ways to breast cancer, the steps in this sequence are neither automatic nor inevitable. The lesions along the varied path to cancer are called "precancerous" or "potential precursors of cancer" but as Foulds observes they are not necessarily predestined to develop into cancer. Actually they are more likely to persist as various types of chronic cystic mastitis or even regress altogether. However, the new property acquired by the

cancer cell in its qualitative and irreversible transformation may now be visibly recognized for the first time by fluorescent staining. With this divining rod "the glories of the possible are ours" for the future.

In summary one may say that there *does* exist a basic relationship between breast cancer and benign breast disease. Certainly the experimental evidence indicates that an endocrine environment prevails which is conducive to the development of both chronic cystic mastitis and breast cancer. The histopathologic studies are strongly suggestive; and the follow-up clinical statistics are indeed most indicative and impressive. In the natural history of breast cancer, chronic cystic mastitis may be only one of several diverse directions in the development of malignancy. The steps of this sequence are discontinuous and are still largely dependent upon the defenses of each individual.

In conclusion, therefore, it must be emphatically stressed that *estrogen therapy* has practically *no* place in the treatment of chronic cystic mastitis. This universal panacea is more often responsible for aggravating the disease than for alleviating it. However, of far greater importance is the stimulating effect (in young women) of estrogens upon a breast cancer mistakenly diagnosed as chronic cystic mastitis. This abuse is a grave clinical error which can result in dire consequences.

Careful follow-up of all patients with chronic cystic mastitis is routinely recommended to every physician who is interested in the proper control of breast cancer. By this means we may be able to discover those small and presumably "early" breast cancers before they have cast their shadows before them—and beyond us.

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Choice of therapy and proper timing are determining factors for the successful management of disseminated breast cancer.

—Dao, T. L.: Management of metastatic cancer of the breast. Exhibit A. M. A. Scientific Assembly. Atlantic City, June 8-12, 1959.

Hypophysectomy in the Treatment of Metastatic Mammary Cancer

Olof H. Pearson, M.D.

The growth of human breast cancer has been shown to be at least partially dependent upon the endocrine environment in many cases. Thus, surgical removal of the ovaries in premenopausal patients will induce objective regression of the metastatic lesions in 40 to 50 per cent of these women. Evidence has been obtained which indicates that the improvement is due to withdrawal of the major endogenous source of estrogens. The remissions induced by castration are temporary, averaging about one year in duration; but this operation, nevertheless, constitutes one of the most effective palliative treatments for the premenopausal patient with metastatic breast cancer.

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These studies were supported in part by grants from the National Cancer Institute, the U. S. Atomic Energy Commission and the American Cancer Society, Inc.

In patients who have had temporary remissions from ovariectomy, removal of the adrenal glands will frequently bring about a further period of improvement. Since the adrenal glands are now known to be an additional source of estrogens, it is believed that improvement induced by adrenalectomy may also be due to withdrawal of estrogens. Combined removal of the ovaries and adrenal glands in *postmenopausal* patients with metastatic breast cancer will induce remission comparable in incidence and duration to those remissions obtained by castration in the *premenopausal* patient. Thus, adrenalectomy is also an effective palliative treatment for many of these patients.

Hypophysectomy was undertaken with the idea that the growth of mammary cancer may also be dependent upon certain pituitary hormones, since it has been established that the growth of the normal breast is dependent upon such factors.

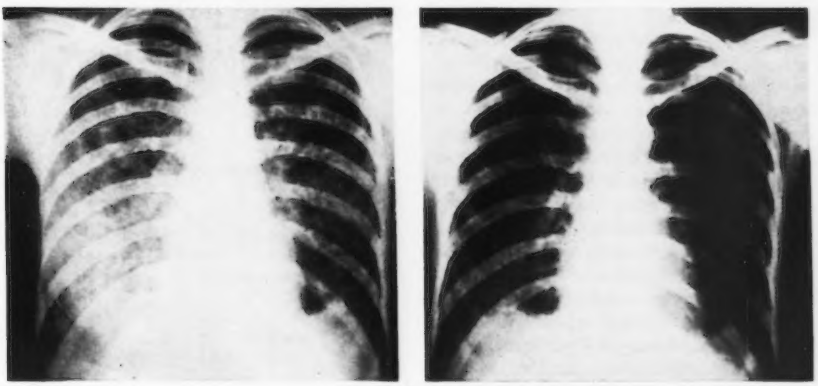

Fig. 1. This 34-year-old, premenopausal patient (a) before hypophysectomy, (b) four months after hypophysectomy, obtained regression of pulmonary and skin metastases after hypophysectomy. Remission lasted 20 months; survival four years and three months.

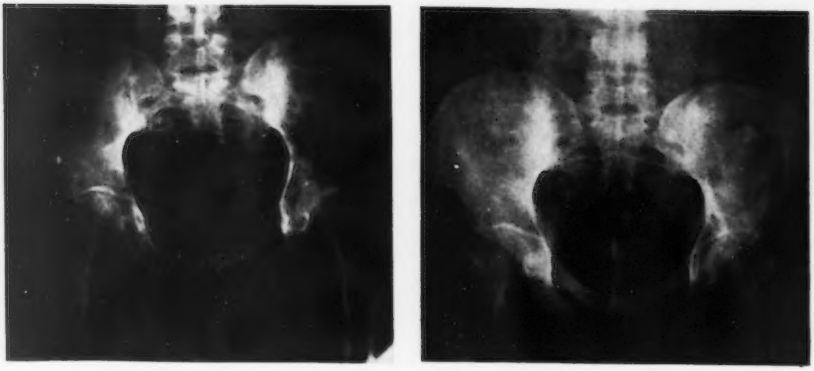

Fig. 2. Osseous metastases from breast cancer (a) before hypophysectomy and (b) nine months after hypophysectomy. This 72-year-old woman was treated prior to hypophysectomy with estrogens that exacerbated the disease; androgens produced a remission for about one year followed by relapse. Patient continues in remission more than two and a half years.

Some evidence has been obtained that suggests that the pituitary may play a role in the growth of breast cancer, but the identity of the presumed factor(s) has not yet been elucidated. Since hypophysectomy produces suppression of the function of the ovaries and adrenal glands, beneficial effects may be due to withdrawal of ovarian and adrenal hormones, as well as the removal of pituitary hormones.

The results of hypophysectomy in 109 patients with metastatic breast cancer will be summarized briefly. Detailed reports of these observations have been published elsewhere.[1] Surgery was performed by Bronson S. Ray by means of a transfrontal craniotomy. All of the patients who underwent hypophysectomy had evidence of advancing disease, and the majority were extremely ill. Most of them had had other forms of endocrine and radiation therapy before hypophysectomy. No attempt was made to select patients. The mortality rate (deaths within 30 days) from all causes was 7.3 per cent. Postoperative complications occurred in 12.9 per cent of the patients, but, for the most part, these disturbances were transient and without residual. Maintenance therapy after surgery consisted of 37.5 mg. of cortisone and 120 mg. of desiccated thyroid by mouth daily. Some patients require posterior pituitary powder by nasal insufflation for control of thirst and polyuria. During periods of stress, the patient requires increased cortisone replacement. This regimen does not constitute a significant burden for the patient. Contrary to some notions, the hypophysectomized patient has a normal appearance and normal mental and physical functions, and he or

Table 1

HYPOPHYSECTOMY RESULTS*

Results	Patients	
	No.	%
Operative Deaths		
Surgery	5	4.6
Cancer	3	2.7
Remission		
6 or more months	38	34.9
Less than 6 months	16	14.7
Failures	47	43.1
Total	109	100.0

*In this group of patients hypophysectomies were performed between March 1954 and September 1956. The table records patient status as of Feb. 1, 1958.

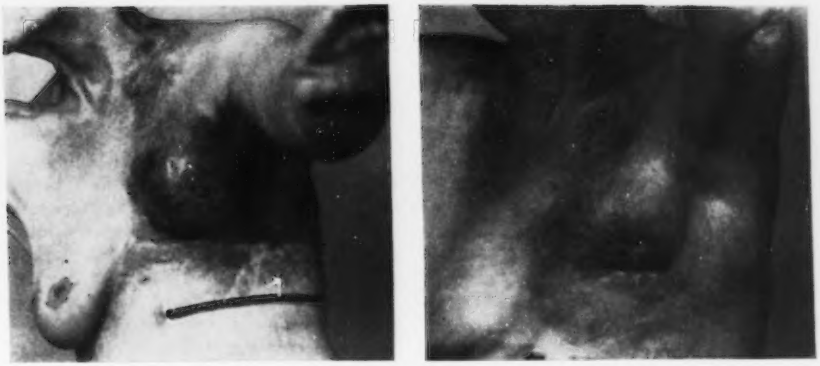

Fig. 3. A 72-year-old woman with inoperable, inflammatory carcinoma of the breast (a) before hypophysectomy and (b) after hypophysectomy. Hypophysectomy-induced remission lasted for nine months, with slow progression thereafter. Death occurred three years after hypophysectomy from coronary occlusion.

she can lead a normal life. Evaluation of the results of hypophysectomy was based on objective evidence of improvement, as evidenced by regression or arrest of the disease.

Table 1 presents the results of hypophysectomy in 109 patients. Fifty-four patients obtained objective remissions; of these, 44 demonstrated regression and 10 demonstrated arrest. Of the 109 patients, 12 had undergone oophorectomy and adrenalectomy prior to hypophysectomy. Four of these 12 were improved. In further experience with hypophysectomy after oophorectomy and adrenalectomy, six of 22 patients have shown objective improvement. Two patients had remissions lasting more than six months, and four had remissions of less than six months' duration. These results appear to be insufficient to recommend hypophysectomy as a therapeutic procedure after oophorectomy and adrenalectomy, but they do suggest that hypophysectomy may add to the beneficial response of some of the patients.

Table 2
RESULTS IN 89 HYPOPHYSECTOMIES*

	Remissions		Failures
	>6 mo.	<6 mo.	
%	42	14	44
Remission			
(Mean)	16.5+ mo.	3.8 mo.	—
(Median)	12.0 mo.	3.8 mo.	—
(Three of 37 patients still in remission.)			
Survival			
(Mean)	24.5+ mo.	9.3 mo.	5.6 mo.†
(Median)	23.0 mo.	8.0 mo.	5.0 mo.†
(Eight of 37 patients still living.)			

*Evaluated to 12/1/58. Twelve adrenalectomized patients and eight patients listed as operative deaths are omitted in this analysis.

†All dead.

Table 2 presents the duration of remission and survival in 89 hypophysectomized patients. Forty-two per cent of these patients obtained objective remissions which lasted six months or longer and averaged 16.5 plus months. Survival time is significantly prolonged in those patients who obtained remissions, as compared to those who failed to benefit. Eight of the 89 patients were premenopausal at the time of hypophysectomy; 29 patients had undergone prior oophorectomy; 11 patients had x-ray castration and 38 were in spontaneous menopause at the time of hypophysectomy. The incidence and duration of remissions did not differ signifi-

cantly in these various groups. The average age of the patients was 50 years, with a range from 28 to 72 years. Objective remissions were obtained in all age groups, from youngest to oldest. The prior response of the premenopausal patient to oophorectomy is of prognostic value in determining the subsequent response to hypophysectomy. Thus, in extended experience, of 15 patients who had transient remissions from oophorectomy, 13 (87 per cent) obtained further improvement from hypophysectomy. Other features, such as the structure of the tumor, the duration of the disease, the age of the patient, the location of the metastases and the response to hormone administration have not proved to be of value in forecasting the response to hypophysectomy in the individual patient.

Figures 1, 2 and 3 illustrate the regression of metastases which may occur in individual patients following hypophysectomy.

These results indicate that hypophysectomy may induce significant remissions and is recommended as a practical, worthwhile procedure in the palliative treatment of patients with metastatic breast cancer when adequate facilities for the procedure are available.

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Suggested Reading

BREAST CANCER AND ITS DIAGNOSIS AND TREATMENT. By Edward F. Lewison, M.D. Baltimore. The Williams & Wilkins Company. 1955.

Together with eight collaborators, Dr. Lewison presents a scholarly, engaging, comprehensive, concise and practical review of the body of existing knowledge of cancer of the breast, female and male: history, anatomy, physiology, pathology, psychology, diagnosis, surgery, radiotherapy, endocrinology, prognosis and statistics. The text and the carefully selected bibliographies with each chapter give the book encyclopedic compass.

Suggested Viewing

AFTER MASTECTOMY

The film, *After Mastectomy*, produced by the Oregon Division of the American Cancer Society, is designed to illustrate the roles played by physician and nurse in the recovery of mastectomy patients. The story in the film concerns a patient from her postoperative period in the hospital to the time she is returned to her home and community. Her feelings and attitudes are described and techniques of handling by physician and nurse are discussed. Both her emotional and physical rehabilitation are considered. The exercises used are those recommended in the American Cancer Society booklet *After Mastectomy* which can accompany the film.

This film is available through your Division of the American Cancer Society. Running time: 20 minutes; 16-mm. color and sound.

Gross Mammary Cysts

Joseph H. Farrow, M.D.

The female breast during the decade from the fortieth to the fiftieth year is the most common of all anatomic sites for cysts of more than one millimeter in diameter.

The principal problem in the diagnosis and treatment of gross mammary cysts is the coexistence or subsequent appearance of other pathological lesions in the breast. Thus, cysts may occur: first, with no significant alteration or atrophy of the mammary epithelium; second, with varying degrees of hyperplastic epithelial changes; and third, within or as a part of a benign or malignant neoplasm of the breast. The coincidence is obvious but the relationship is controversial and obscure. The functionless and rudimentary male mammary gland is subject to most of the diseases that are peculiar to the female breast but gross cysts are conspicuously absent.

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History. The first important description of mammary cysts was published in 1840 by Brodie. It is generally considered one of the medical classics and the frequently quoted portions of this article are:

"The disease of which I propose to treat on the present occasion, is an affection of the female breast. It is one of great interest in various ways, and among others in this: that in its more advanced stages,

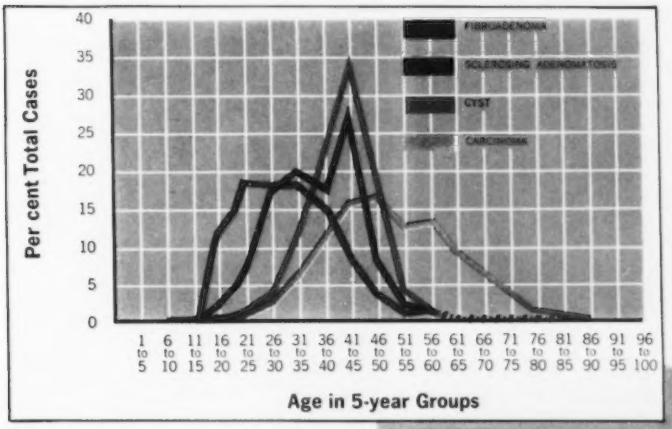

Fig. 1

Fig. 1. Age distribution of gross cysts, other benign lesions and cancer. All verified either by aspiration or surgery.

Fig. 2

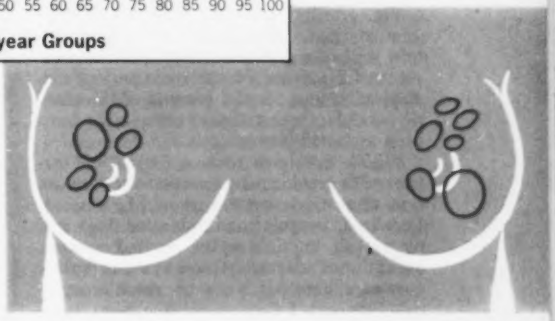

Fig. 2. Multiple gross cysts treated by aspiration over a nine-year period. E. M., a 43-year-old childless patient, had irregular menses initially but was amenorrheic for past seven years after hysterectomy for fibroids.

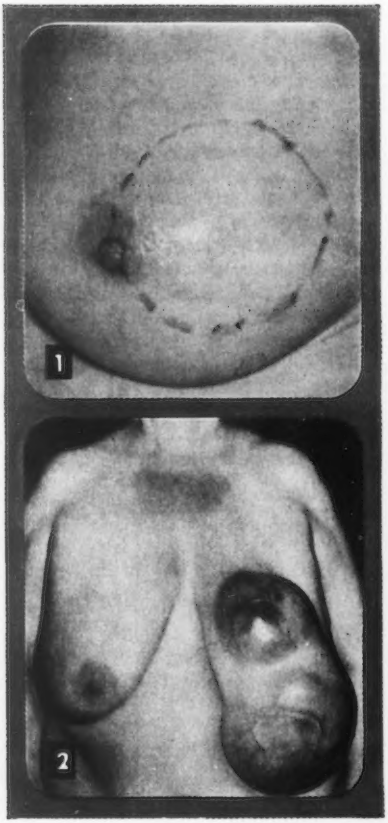

Fig. 1. Age 50, unmarried, regular menses; mass in left breast for two weeks. Tensely cystic and movable mass measured 12 cm. in diameter. Transillumination clear. 120 cc. fluid obtained on aspiration. Second cyst aspirated nine months later; excision localized lesion along radius 12 o'clock. Path. rep.: Cyst, papillomatosis and sclerosing adenosis. No evidence of disease four years later.

Fig. 2. Age 70, married; enlargement of left breast for eight years; large discrete cystic masses filling entire breast with recent ulceration of skin over a small area; simple mastectomy. Path. rep.: Multiple large cysts each containing intracystic papillomas. (Courtesy Dr. A. I. Holleb.)

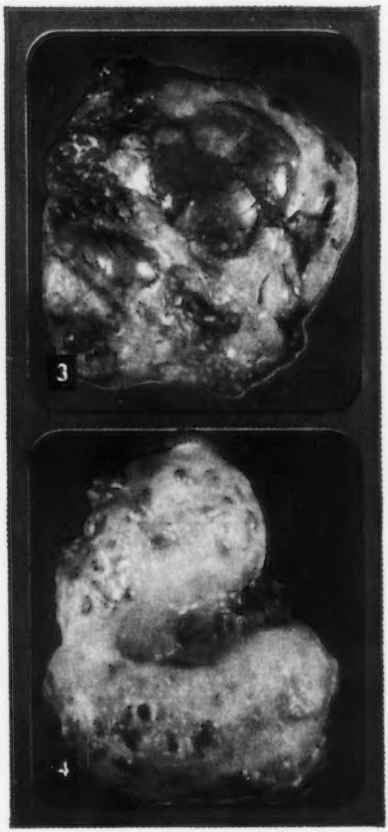

Fig. 3. Specimen from a 42-year-old patient, married, demonstrating multiplicity and thin wall of gross cysts which presented on the under surface of the mammary gland. Aspiration unsuccessful because of thickness of overlying breast tissue; other cysts have been aspirated subsequently.

Fig. 4. Specimen from a 34-year-old patient with regular periods, demonstrating the type of cystic lesion that should be excised. Localized, irregular and indurated 5×3 cm. mass with multiple cysts; excised without aspiration. Path. rep.: Gross cysts; extensive duct papillomatosis, some of which is atypical. Frequent follow-up examinations have been negative.

Fig. 5. Specimen showing gross cysts occurring in one of two fibroadenomas removed from the left breast of a 40-year-old unmarried patient with regular menses. Subsequently, at various times, cysts have been aspirated containing straw-colored fluid from both breasts.

Fig. 6. This 38-year-old patient with a history of regular menses presented a 4-cm. circumscribed, fluctuant and freely movable mass in the right breast on examination; shadow on transillumination. When aspirated bloody fluid was obtained; local excision. Path. rep.: Intracystic papilloma. Ten years later, an infarcted fibroadenoma was excised from the same breast.

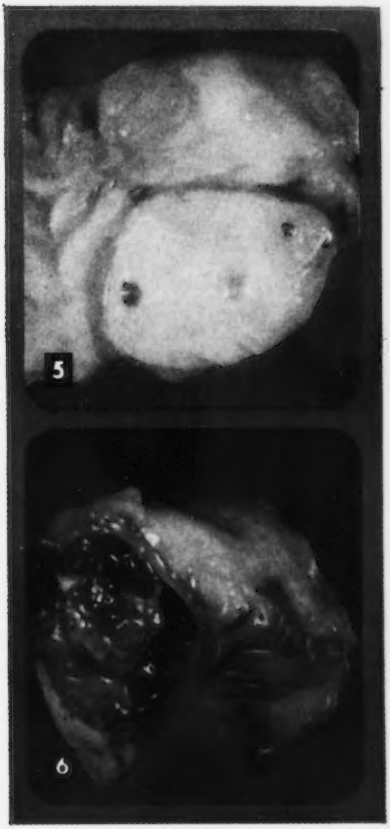

Fig. 7. Age 32, married. Bloody discharge from left nipple (3/28/42); excision of duct system. Path. rep.: Hyperplastic ducts. Circumscribed 4-cm. mass near scar; local excision and modified radical mastectomy. Intracystic papillary carcinoma (3/12/46). No evidence of disease seven years later.

Fig. 8. Specimen from a 47-year-old unmarried patient demonstrating the coexistence of gross cysts and cancer. During six-year period multiple and bilateral cysts were aspirated. Then, aspiration of a clinical cyst failed to reveal fluid; local excision and radical mastectomy. Path. diag.: Infiltrating duct cancer with metastases to a single axillary lymph node.

although it is not really of a malignant nature, it is liable to be confounded with carcinoma. I have not met with any description of it in books corresponding to what I have myself observed of its actual progress. You will presently see that this is easily to be explained by the disease assuming a wholly new character as it proceeds, so that if you were to look at two cases of it, one in an early, and the other in a more advanced stage, without having witnessed the intermediate changes which have taken place, you would be scarcely able to recognize their identity. Let me not, however, be misunderstood as representing that no notice whatever has been taken of this disease by surgical writers. The account which Sir Astley Cooper has given of the hydatid breast has been taken principally from cases of this kind, and there are also allusions to it in the *'Treatise on Disease of the Breast,'* lately published by M. Velpeau.

"The first perceptible indication of the disease is a globular tumour embedded in the glandular structure of the breast, and to a certain extent movable underneath the skin. Sometimes there is only one such tumour; at other times there are two or three or many more. The examination of the breast in the living person does not enable you to determine the exact number which exist, as it is only where they have attained a certain magnitude that they are perceptible through the skin. In most instances the disease is confined to one breast, though it is by no means very uncommon for both breasts to be similarly affected.

"The globular form which the tumour invariably assumes in the first instance, is a sufficient proof that it is formed of fluid collected in a cyst, and of course pressing equally in every direction. If you puncture the tumour with a grooved needle, the fluid may be evacuated so as completely to empty the cyst, and the perfect subsidence of it afterwards proves how little space the cyst itself occupies. The fluid is always serous. When the tumour is small it seems to be serum, unmixed with anything else. In a more advanced stage of the disease, some colouring matter is generally blended with it, and it may be green, or brown, or so dark-coloured as to be almost black. The quantity of fluid of course varies. In dissection, I have sometimes found the cyst to be so small as to contain scarcely a single drop. But in a more advanced stage it is capable of containing several ounces. In two cases, in each of which I had the opportunity of dissecting a breast affected with this disease, I found small cysts, composed of a thin membrane, and containing serum, pervading the whole of the glandular structure, the intermediate parts of the breast presenting a perfectly healthy and natural appearance; and I could discover nothing more. There seems to be little doubt that the cysts are originally formed by a dilatation of the lactiferous tubes.

"To complete the history of the disease, as it first shows itself, I may add that the general health is unaffected, and that the patient complains of no pain, unless it be that, in some instances, there are those disagreeable nervous sensations that are apt to arise whenever the attention is anxiously directed to any one part of the body. I have never known the disease to occur previously to the age of puberty; it is rare after the middle period of life, and I am inclined to believe it is more common in single than in married women."

Although Brodie suggested the term "sero-cystic tumour," the condition was subsequently referred to as Brodie's tumor or disease. Forty-three years later Reclus redescribed mammary cysts, emphasizing the multiplicity and bilaterality of the lesions along with the hyperplastic changes of the breast epithelium. The variations and complexity of the cystic environment rather than the mammary cysts per se have been the subject of numerous publications. Many authors have sought to provide a more exact terminology. From the literature Deaver and McFarland collected 24 different terms which they stated would harmonize to varying degrees. Other terms have since been added but have not been generally accepted. Ironically, one of the least descriptive terms, "chronic cystic mastitis," suggested by

König in 1893, has survived and is the one most commonly employed today.

Etiology. The factors which predispose to the formation of cysts are not entirely known. Despite the absence of control data, it is apparent from observations that celibacy or pregnancy with failure to nurse can play only a relatively minor role, if any. Blockage of terminal ducts with isolation of cells may follow periductal fibrosis or intrinsic proliferations or a combination of these conditions. Just why secretory activity occurs in some but not all of these obstructed and isolated areas of a nonfunctioning mammary gland has not been determined. The average age of the patients, the secretory activity and the multiplicity and bilaterality of the lesions suggest a hormonal disturbance. The exact nature of the disturbance, however, has not been assayed and efforts to control mammary cysts by the empirical administration of synthetic hormones have shown no noticeable clinical benefit.

Symptoms and Physical Findings. There is little need to add to the previously quoted description by Brodie. Most cysts are asymptomatic and discovered by accident or during a routine examination. When the cysts are very large and tense, patients may complain of a transient sticking or burning sensation, a sense of heaviness or a slight increase in the size of the breast. There is rarely a nipple discharge or noticeable alteration of the contour of the breast. Gross cysts may sometimes appear quite suddenly and enlarge rapidly while at other times they may increase in size slowly or show little change.

Visual inspection of the breast is essentially negative since cysts are almost uniformly detected by palpation. Physical findings usually reveal a discrete, movable, nontender and rounded mass. The lesions may be singular but most often are multiple and frequently bilateral. Fluctuation will vary according to the relative size of the cyst and the breast, thickness of the cyst wall and the location within the mammary gland. Cysts are rarely found immediately beneath the nipple.

Diagnosis. The principal lesions which may be clinically confused with gross cysts are as follows: (1) lipoma; (2) fibroadenoma; (3) well-circumscribed carcinoma; (4) intracystic papilloma or cancer; (5) nonpuerperal abscess. Briefly, lipomas are relatively soft, superficial to the glandular portion of the breast and commonly associated with a generalized lipomatosis. Fibroadenomas are nonfluctuant, single more often than not and occur in younger women, in whom gross cysts are relatively uncommon. Circumscribed carcinomas are single and may show skin attachment and axillary adenopathy. Nonpuerperal abscess within the mammary gland and intracystic benign and malignant neoplasms are so rare that clinical differentiation is extremely difficult.

Transillumination for suspected cysts serves a two-fold purpose. First, a cyst containing clear or straw-colored fluid gives a typical rounded area of translucence. A cyst containing opaque liquid may cast a shadow indistinguishable from that of a localized noncystic tumor. Second, if aspiration is attempted, transillumination will demonstrate subcutaneous veins in the region of the lesion and thus enable one to avoid puncturing these vessels. The intensity of the light should be regulated according to the size of the breast. Transillumination as a rule reveals little if the lesion is less than 0.5 cm. in diameter.

Radiographic examination of the breast is of doubtful value since cysts demonstrable by this means are easily palpable.

The most practical diagnostic procedure is the aspiration biopsy. The diagnostic advantages of tapping, acupuncture or aspiration of selected subcutaneous or organic lesions, without or, as more recently, with cytological studies of aspirated material, have been recognized for over a hundred years but the procedure is still unjustly condemned or misused by some authorities. With particular reference to gross mammary cysts it is both a diagnostic and therapeutic measure.

Treatment. Since the time that gross cysts were described in detail, opinions as to the best treatment have been and still are divided. With extremely few excep-

tions, the ultra-conservative approach of observation is condemned. Only patients showing multiple and diffuse unilateral and bilateral 1-to-5 mm. rounded lesions, without other physical findings and without positive proof of fluid contents, should be observed. In these cases it is particularly urgent to stress the need for frequent routine self and professional examination.

Conservative treatment by simple aspiration was an early form of therapy and practiced by Velpeau, who recommended the injection of an irritating solution (iodine) to destroy the sac. Without the injection of sclerosing or irritating solutions, aspiration has been widely employed and, if its limitations are recognized, it is the procedure of choice today.

The technique and equipment used in aspirating fluid are slightly different from those employed for the removal of tissue. After suitable preparation of the skin and with, or usually without, local anesthesia, one can easily puncture and withdraw the fluid of a cyst, using a 19- or 20-gauge intramuscular needle and an ordinary 5 or 10 cc. syringe. It is important to remove the fluid completely because incomplete removal leaves a residual mass and will cause prompt refilling of the cyst. Immediately after aspiration a small compression bandage is applied for 24 hours. This prevents subcutaneous ecchymosis and maintains collapse of the cyst cavity. Cytological examination of aspirated nonsanguineous fluid has proved of little value and is rarely done. The size and multiplicity of the cysts and the physical status of the remaining breast tissue should determine the interval and duration of follow-up examinations. For the average patient intervals of one to three months during the first year seem adequate.

The principal advantages of therapeutic aspirations are that they require no hospitalization and avoid either multiple or consecutive operations. There are obvious limitations, since one does not know what may remain in the mammary gland. The following situations demand local excisions: first, failure to obtain fluid; second, bloody fluid; third, residual mass after fluid removal; and fourth, prompt and persistent refilling of a cyst.

Surgical excision of single and multiple cysts is the preferred treatment by some surgeons. It should be used when there is a question regarding pathological changes in the surrounding breast tissue. Localized areas of increased density with poor marginal definition but clinically containing gross cysts should be removed. This is particularly true in young women with gross cysts, for experience has shown they have a high incidence of epithelial hyperplasia. Few surgeons now perform a simple mastectomy for multiple gross cysts and, except for rare special circumstances, this operation is usually avoided. Surgical sampling by simply removing one of many cysts and then aspirating others seems unnecessary.

Cancer and Gross Cysts. The benign nature of gross mammary cysts has been recognized since they were first described. If they do play a role in the development of cancer it is an essentially negative one and is limited to those relatively rare cysts which contain intracystic hyperplasias. On the other hand, the cystic environment has deserved the exhaustive studies that have been made with a view to establishing a relationship with cancer.

Modern authorities believe there is an added cancer risk when coexistent hyperplastic changes are found in the mammary epithelium. Extremely few, however, propose either unilateral or bilateral prophylactic mastectomies. There are at hand neither sufficient statistical data nor reliable means to predict which patients will eventually develop cancer. Certainly, there is no justification to populate the world with surgical St. Agathas.

Summary

Gross cysts are the most common lesions of the breast at the time immediately preceding and during the menopause. The cysts are usually multiple and frequently bilateral. With limitations, simple aspiration is the treatment of choice. It should be borne in mind that gross cysts in some instances are a part of and not the complete pathological process. Further, multi-

plicity and bilaterality, although indicative of benign lesions, by no means completely exclude the existence of cancer. Finally, in our efforts to be conservative we should not forget that uncertainty is one of the indications for surgery.

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1:17,	Nov.,	1950	Modes of breast-cancer spread: they determine treatment and diagnosis.
1:22,	Nov.,	1950	Cancer clinic; cancer of the breast.
1:30,	Nov.,	1950	Breast-examination.
1:86,	March,	1951	Sex hormones in breast cancer.
1:181,	Sept.,	1951	Value of genetics for earily diagnosis of cancer.
1:195,	Sept.,	1951	Breast cancer in mother and daughter.
2:156,	Sept.,	1952	St. Agatha, the patron saint of diseases of the breast.
2:160,	Sept.,	1952	The examination of the breasts.
2:162,	Sept.,	1952	The physician's examination in cancer of the breast.
2:166,	Sept.,	1952	Diagnosis of localized breast cancer from the standpoint of the general practitioner.
2:169,	Sept.,	1952	Cancer clinic; cancer of the breast.
3:188,	Sept.,	1953	The diagnosis of early carcinoma.
3:190,	Sept.,	1953	Cancer clinic; cancer of the breast.
3:205,	Sept.,	1953	Periodic examination of the female pelvic organs and breast.
4:160,	Sept.,	1954	Benign lesions of the breast.
4:191,	Nov.,	1954	The value of exfoliative cytology in the diagnosis and control of neoplastic disease of the breast.
4:198,	Nov.,	1954	Muscle training after mastectomy.
4:200,	Nov.,	1954	Carcinoma of the breast.
4:206,	Nov.,	1954	Cancer clinic; management of carcinoma of the breast.
6:54,	March,	1956	Important steps in examining the breasts.
6:58,	March,	1956	Breast cancer and the general practitioner.
6:61,	March,	1956	Cancer of the male breast.
6:66,	March,	1956	Cancer clinic; cancer of the breast.
6:96,	May,	1956	Palliative medical therapy of cancer.
6:99,	May,	1956	Kinescope: the diagnosis of breast cancer.
6:135,	July,	1956	Cytology of nipple secretions.
8:16,	Jan.-Feb.,	1958	Benign and malignant lesions of the nipple.
8:20,	Jan.-Feb.,	1958	Radical mastectomy with en bloc in continuity resection of the internal mammary lymph-node chain.
8:27,	Jan.-Feb.,	1958	Precancerous lesions of the breast.
8:32,	Jan.-Feb.,	1958	Cancer clinic; carcinoma of the breast.
9:98,	May-June,	1959	Case report: cystosarcoma phyllodes.

The Management of Patients with Advanced Breast Cancer

Frances H. Trimble, M.D.

So many conflicting reports have appeared over the past few years on the efficacy of treatment in primary breast cancer, that it is difficult even for those closest to the field to reconcile the discrepancies in results. Two broad generalizations emerge from the welter of facts and figures: firstly, if the lesion is considered operable, regardless of age, radical mastectomy offers the patient the greatest hope of benefit, even though not every individual cancer cell may be eradicated. Secondly, there are many variables governing the survival time of a given patient, but as yet no one is wise enough to assess the factor of host resistance in predicting a prognosis. We know that in the majority of women dissemination will ultimately occur, with fatal outcome, but this is no reason to adopt a defeatist attitude and deny the patient the various forms of palliative therapy which often lead to tumor regression and almost always give symptomatic relief.

Radiotherapy

Usually the first mode of treatment to be considered in advanced, inoperable or recurrent breast cancer is irradiation. Especially is this the treatment of choice in the clinical entity described as "inflammatory carcinoma" in which irradiation, endocrine treatment and oophorectomy give better results than mastectomy. Local therapy frequently is most helpful in healing ulcerated and bleeding local lesions involving the breast and chest wall. Radiotherapy can be given more effectively if the bulk of breast tissue is removed by simple mastectomy, but this is not always warranted nor advisable. In such patients it is customary to treat only those areas with overt disease, as distant metastases are almost certainly present and it is important to avoid the discomfort of a severe local reaction. In approximately 40 per cent of patients the site of first metastasis after radical mastectomy will be either in the operative area or in the supraclavicular nodes,[1] and these frequently respond well to x-ray therapy. In 31 per cent of patients the first metastasis will involve a bone, most frequently the ribs, vertebrae and pelvic girdle. Irradiation gives prompt relief of pain in weight-bearing areas in about 75 per cent of such patients, and is always indicated for this reason, even if multiple metastases are present. Bone pain may precede x-ray evidence of destruction by several months.

There are, however, limitations to the use of x-ray treatment. Prolonged treatment to the chest wall may affect the vitality of normal tissues and produce radionecrosis. Radiation pneumonitis and fibrosis may occur in the underlying lung fields, with resultant cough, dyspnea and systemic effects that are difficult to treat. There may also be destruction and depression of bone marrow with anemia following prolonged treatment. A pleural effusion can often be relieved by thoracentesis and the instillation of radioactive colloidal gold into the pleural cavity.

Some institutions have facilities for supervoltage radiation, delivered either by a machine of a million volts or more, or by a cobalt unit. With this type of therapy, an effective dose can be given with less risk of complications and over a shorter period of time with less discomfort to the patient. However, as with conventional x-ray therapy, the effect is entirely local.

Hormone Therapy

The concept of hormone therapy is based on the well demonstrated dependence of mammary tissue on hormone stim-

From the Johns Hopkins Hospital, Baltimore, Maryland.

ulation. Experimental evidence suggests that progressive growth in breast cancer is under the control of the same group of hormones that influence normal mammogenesis. These are the anterior pituitary hormones prolactin or mammotropin and the growth hormone or somatotropin; and the ovarian hormones estrogen and progesterone, with some assistance from the adrenal corticoids. Neoplasia results when cell growth is unrestrained due to a combination of factors, but undoubtedly one of the most potent of these is hormonal derangement. Hormonal carcinogenesis is probably due to a disproportion between pituitary and ovarian hormones. It seems likely that most breast tumors go through a stage of hormone dependency, but later become autonomous. For this reason various methods of altering the endocrine status of the patient have been tried in an effort to control the disease once metastases have become evident. These fall into two categories: ablative, by oophorectomy, adrenalectomy or hypophysectomy; and additive, employing androgens, estrogens and corticosteroids (cortisone, dexamethasone or prednisone).

Castration

This is usually the first step taken in a premenopausal woman presenting with recurrent disease. Surgical castration is probably the surest method of treating a patient under forty years of age; there is a rapid drop in urinary estrogens, with resultant shift in vaginal cytology. It was thought for a while that those patients with cortical stromal hyperplasia of the ovaries showed the best response to operation, but this no longer appears valid. One advantage of oophorectomy is that future pregnancy cannot possibly occur. Roughly one third of these patients show a good response with regression in soft tissue and bony lesions which may be maintained for as long as a year. In patients more than forty, it is usually possible to suppress ovarian function by pelvic irradiation, although the clinical effect is slower and less certain. Regression probably does not occur as frequently as the patient is approaching the menopause.

Castration in the male patient seems to be effective in a larger proportion of patients irrespective of age.

Adrenalectomy

It has been demonstrated in experimental animals that following castration there is hyperplasia of the adrenals, and certainly there is persistent urinary excretion of estrogenic compounds in patients subjected to oophorectomy. For that reason bilateral adrenalectomy has been recommended when progression follows a remission induced by castration or persists in spite of castration. A careful study has just been completed by Block and his co-workers, at Ann Arbor, with an American Cancer Society grant, into the problems of adrenalectomy. They recommend limiting the operation to patients of "middle age" with an interval of over three years following mastectomy; in whom previous remission has followed oophorectomy, but who still maintain high urinary estrogens; and in whom no liver metastases are present. In a selected series such as this, half of the patients will be improved and 25 per cent will remain in remission for a year or more. However, one must face the fact that the remaining unresponsive patients have a surgically induced Addison's disease and both groups must remain on daily cortisone for the duration of their lives, needing careful medical supervision.

Hypophysectomy

This operation has been performed in many centers over the past few years, but the most impressive results are those obtained by the Scandinavians Luft and Olivecrona, and in the United States, by the Memorial Hospital (New York) group. The latter tend to consider this form of surgery early in recurrent disease. By this operation mammotropin and the growth promoting hormone of the pituitary are eliminated and in addition there is profound suppression of ovarian and adrenal function. There is often a dramatic

relief of pain, as well as objective tumor regression, and in some instances life has been prolonged for many months. This operation is not considered if liver or brain metastases are present. Hypophysectomy can also be attempted by the transcranial or trans-sphenoid implantation of radioisotopes, as yttrium-90. Following hypophysectomy, supportive therapy is necessary in the form of 50 mg. of cortisone daily, pitressin by insufflation or injection to control the diabetes insipidus and oral thyroid to prevent myxedema.

ANDROGENS. Androgens may be used at any age but are the hormone of choice in patients in the premenopausal, menopausal and up to five years postmenopausal groups. About 25 per cent of patients respond to this form of therapy, with remissions which average about seven months. Where a favorable response occurs the patient lives twice as long as the unresponsive patient. In most patients there is marked subjective improvement, with an increase in the sense of well-being, probably due to the protein anabolic effect and to the stimulation of haemopoiesis. There may be striking regression in bone and soft tissue metastases but this is less likely in visceral metastases. Treatment is best given by means of testosterone propionate 100 mg. three times weekly and continued for six to eight weeks to evaluate the therapeutic effect: if no response occurs, sometimes improvement follows withdrawal of the hormone. If the response is favorable, treatment should continue until maximum regression is obtained. Methyl testosterone, given orally, sometimes causes liver damage and is not the drug of choice. The side effects of androgen therapy, although all do not occur in every instance, are usually distressing to the patient. These include hirsutism, deepening of the voice, acne and increase in libido. Hypercalcemia is rarely a problem in younger, ambulatory patients. Acceleration of the disease can sometimes follow androgen therapy, perhaps due to conversion to estrogens in the body.

ESTROGENS. A good rule to follow is that estrogens must never be given to patients less than five years postmenopausal. Their greatest benefit is in the older age range, and at least 40 per cent of patients experience regression. Sometimes healing is noticed in bone lesions, but their principal effect is in advanced primary disease, soft tissue and visceral metastases. Dramatic shrinking can occur both in lesions of the chest wall and in lung metastases. As with androgens, an empiric trial period of six to eight weeks should be set and treatment continued until the disease is apparently quiescent. Estrogens can be given as ethinyl estradiol 3 mg. daily, or diethyl stilbestrol 15 mg. daily; the latter compound can be obtained in enteric coated tablets which is helpful if nausea results from estrogen therapy. Nausea can often be avoided by a gradual increase in dose schedule or by antiemetic agents. Pigmentation of the nipple and areola usually appears early in treatment. Edema may be a problem due to fluid retention, but has been found to respond readily to fluid restriction and the use of chlorothiazide, one

SEQUENCE OF TREATMENT FOR ADVANCED BREAST CANCER*

PREMENOPAUSAL

1. Castration

Remission	*If no remission*
2. Androgens	2. Androgens
3. Corticosteroids	3. Hypophysectomy
4. Hypophysectomy	4. Chemotherapy
5. Chemotherapy	

MENOPAUSAL AND UP TO 5 YEARS POSTMENOPAUSAL

1. Androgens

Remission	*If no remission*
2. Costicosteroids	2. Oophorectomy and adrenalectomy
3. Hypophysectomy	3. Corticosteroids
4. Chemotherapy	4. Hypophysectomy
	5. Chemotherapy

POSTMENOPAUSAL

1. Estrogens

Remission	*If no remission*
2. Androgens	2. Androgens
3. Corticosteroids	3. Corticosteroids
4. Chemotherapy	4. Chemotherapy

**Breast Clinic, Johns Hopkins Hospital*

or two 500 mg. tablets daily. If congestive failure supervenes, the use of digitalis seems to be both therapeutic and synergistic in effect. Vaginal bleeding occurs more often as a withdrawal symptom than accompanying therapy.

ADRENAL STEROIDS. Cortisone has been used in an attempt to effect a chemical adrenalectomy by means of adrenocortical suppression. However, it has the effect of stimulating the release of the follicle stimulating hormone from the pituitary, so in patients under sixty years of age its use should only follow oophorectomy. This form of treatment can be used in patients in whom androgens and estrogens have proved ineffective. Any favorable effect is usually short-lived. Lemon has recently substituted the use of prednisone in a dosage of 30 mg. daily, with thyroid, and feels that his percentage (39.5) of objective remissions equals that obtained with the oophorectomy-adrenalectomy sequence or with hypophysectomy. A trial of prednisone in this dosage or dexamethasone 3–4 mg. daily is worthwhile in the presence of brain or liver metastases. Fluid retention usually becomes a problem but is diminished by chlorothiazide.

Chemotherapy

Ultimately far advanced neoplastic disease will cease to respond to so-called conventional therapy as outlined above, and recourse can be made to derivatives of nitrogen mustard, which are alkylating compounds. These agents cause a severe disruption of mitosis and so are injurious to cells which divide frequently—hence their depressant effect on bone marrow. The largest series reported is that of Bateman, who used thioTEPA (triethylenethiophosphoramide) by intramuscular, intravenous, intrapleural, intraperitoneal, intratumor and oral routes. About two thirds of the patients showed some objective improvement, lasting approximately eight months. This form of treatment has been used with some success in liver metastases and where pleural and peritoneal effusions are present. The principal drawback is the bone marrow depression with anemia, leukopenia and drop in platelets. Obviously close supervision and frequent blood counts are necessary.

A recent attempt to combine hormone therapy and chemotherapy has been reported by Watson and Turner in England. They decided to alter the hormone environment by combining oophorectomy and testosterone administration, adding to this the antimitotic activity of thioTEPA. [See abstract p. 150.] They reasoned that the protein-anabolic effect and stimulation of hemopoiesis by the androgens might offset the depression of bone marrow induced by the alkylating agent. Their results are encouraging and the rationale of synergistic therapy warrants more extensive trials.

Summary

The table outlines the sequence of treatment used in the various age groups in the Breast Clinic of the Johns Hopkins Hospital. Much can be offered to these patients and it is most important that the patient and her family should never be allowed to feel that the physician has given up hope. In deciding between the ablation procedures and the administration of hormones or chemotherapy, one must temper enthusiasm with clinical judgment and consider the patient's family and financial situation before involving them in the heavy costs of hospitalization followed by complicated and costly substitution therapy, when no cure can honestly be promised. Nothing is lost by a trial of conservative therapy, which can be conducted at home under the supervision of the family doctor.

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CANCER CLINIC

Consultation by Correspondence

Replacing the usual Cancer Clinic in this issue is the following account of a medical problem presented in a letter to the editor and referred to several consultants.

Referring Physician:
Dr. Virginia Downes

A 78-year-old physician with diagnosis of many years standing of chronic lymphatic leukemia has now a white cell count of 30,000, with 60 to 70 per cent lymphocytes. Two years ago nodules appeared in the neck and later in the elbow and groin. These were diagnosed by the pathologist as malignant lymphosarcoma and have responded very well to small dosage x-ray therapy. X-ray examinations of the chest were consistently negative until May, 1958 when a lesion was noted in the right lung. About the same time a pathological fracture occurred in the right clavicle. With increasing spread of the lung lesion a small dose of radiation was given to the right lung producing a severe physical reaction. Sputum examination was reported to show tubercle bacilli on slide, in culture and upon animal inoculation. Bronchoscopy four months later yielded the impression that the lesion was not tuberculosis but a neoplasm of some type not necessarily related to the lymphatic leukemia. Sputum examination for tuberculosis was repeated at different laboratories after the patient had been on para-aminosalicylic acid and isoniazid therapy. These examinations were reported variously as negative, as containing photochromogens and as being positive for tubercle bacilli. Animal inoculation is now in progress.

Should this patient be given a course of nitrogen mustard now? There has been a weight gain of about a pound a week. Anemia (8 gm. hemoglobin) has been corrected through cell mass transfusion. Roentgenograms taken in August and in December showed some extension of the mass. Physically the patient appears well and is without fever or cough. In the management of this case, what further therapy should be planned, and should the patient be isolated?

Hematologist:
Dr. William Dameshek

A very difficult situation. Appearance of lymphosarcoma nodules in course of chronic lymphocytic leukemia is unusual but does occur and poses many therapeutic problems more difficult than therapy for the chronic leukemia alone. The pulmonary lesion is almost certainly lymphosarcoma, perhaps contaminated with tuberculosis which not infrequently develops in chronic lymphocytic leukemia after some years—old infection, lack of defenses, etc. Advise an alkylating agent. Nitrogen mustard would be the quickest and most likely to cause regression of the mass. Leukeran would be a slower, more cautious method, but might in time result in improvement. Steroids often have a dramatic effect in these cases, but one supposes, in view of finding tuberculosis, that these are not indicated. Still they might be reserved for future therapy, especially in view of anemia, plus adequate coverage with antituberculosis measures.

Phthisiologist:
Dr. Arthur B. Robins

I do not believe I can provide definitive answers to the questions raised in

your letter. Part of my difficulty relates to the equivocal nature of the findings, and part to the many associated factors which would govern decisions of this type. The latter cannot be made satisfactorily without actually knowing more about the patient and her circumstances than is indicated in your communication.

One of the basic difficulties is the various reports on the sputum from different laboratories. Obviously, the management of the patient will depend a great deal on whether the sputum contains tubercle bacilli, atypical acid-fast organisms or is abacillary. In view of the uncertainty, the isolation of the patient at present would definitely seem to be indicated. This may already be accomplished for all practical purposes in a 78-year-old physician not in practice even if she is not hospitalized. As regards further therapy for the tuberculosis, this too will probably have to await a more definitive decision about the bacteriological findings. Assuming that the latter is positive and that the pulmonary lesion has a tuberculous component and the initial therapy has been carried on long enough to warrant the conclusion that it is not effective, one might add streptomycin to the regimen.

Regarding the management of the nontuberculous condition, I would not be inclined to use nitrogen mustard at this point. The brief references to her clinical state would seem to indicate that it is satisfactory at this moment. This would strongly influence me to let well enough alone in a woman of this age.

Hematologist:
Dr. Richard A. Marshall

The illness of the patient to whom you refer is quite complicated, and it is difficult to draw definitive impressions without actually examining the patient. The diagnosis of chronic lymphocytic leukemia seems well established by the long history of a leukocytosis with increased numbers of lymphocytes, anemia and the node biopsy diagnosis of malignant lymphosarcoma two years ago. The clinical or pathologic differentiation of chronic lymphocytic leukemia from small cell lymphosarcoma is nearly impossible and we tend to treat them the same. Although lymphocytic leukemoid reactions have been reported in miliary tuberculosis and carcinoma of the breast and sigmoid, it is unlikely that this patient's blood picture is a result of the pulmonary process because of the temporal relationships. In the primary disease process of chronic lymphocytic leukemia the real issue is whether the pulmonary and skeletal lesions can be accounted for by the primary disease. From the information available, the diagnosis of pulmonary tuberculosis is strongly suggested by the presence of tubercle bacilli on sputum smear, culture and animal inoculation. Tuberculosis and fungal infections complicating leukemia or lymphoma are frequently observed. However, a mass in the lung which spreads on adequate antituberculous chemotherapy is a strong point against the tuberculous nature of the lesion. The impression of a neoplasm other than leukemia or lymphoma made at bronchoscopy is worthy of further investigation. Although pathologic fractures have been reported in adult patients with chronic lymphocytic leukemia, the right clavicular lesion may represent bony metastasis from a bronchogenic carcinoma.

The following is a list of suggestions for further diagnostic studies and therapy:

1. A right scalene fat pad biopsy with biopsy of the right clavicular lesion should be helpful in establishing the nature of the right pulmonary mass.

2. Drug sensitivity studies on the tubercle bacilli isolated from the recent cultures will help guide future antituberculous chemotherapy.

3. The nature of the anemia should be further investigated to determine if there is a major hemolytic component such as spherocytes, increased osmotic fragility, Coombs' test or reticulocytosis. If this does appear to be a hemolytic anemia, I would not favor corticosteroid therapy because of the danger of spread of the tuberculosis.

4. If the nature of the right pulmonary mass appears to be lymphoma or leukemia, I would cautiously give a course of chlorambucil or triethylenemelamine since

patients with chronic lymphocytic leukemia sometimes tolerate poorly the usual doses of nitrogen mustard. If the pulmonary mass appears to be a bronchogenic carcinoma, nitrogen mustard might be used, although the results in histologic types other than oat cell are seldom good.

Medical Oncologist:
Dr. Lloyd F. Craver

In the case described in your letter I would suspect that the patient not only has lympholeukosarcoma and pulmonary tuberculosis, but may also have another neoplasm in the lungs such as bronchogenic carcinoma. If all this is true the treatment would be most difficult. I would think she should be maintained on antituberculosis therapy. She may require spot treatment with radiation from time to time, depending on what lesions of the lymphosarcoma appear. Steroids probably should be avoided if possible in view of the strong suspicion of tuberculosis, and if they have to be resorted to, certainly antituberculosis therapy should be vigorously maintained. In regard to use of an alkylating agent, I think I might be more inclined to suggest a prolonged course of chlorambucil with close watch on the blood-cell count, especially the white cells and platelets, rather than to give nitrogen mustard.

Referring Physician:
Dr. Virginia Downes

Thank you very much for sending us copies of the consultants' opinions. I read them with a great deal of interest and would be very happy to have the case discussed further in your very excellent medical journal. Some additional facts might be of interest. Since I first wrote, the initial cultures in October have been reported as positive to guinea pig inoculation. Many subsequent sputum cultures have all been negative with the exception of one in December, which is being confirmed by guinea pig inoculation at the present time. The patient has gained fifteen pounds. Her white cell count is now 5,000. A distressing tendency to recurrence of her anemia is corrected by twice monthly transfusions of cell mass. She continues to receive antituberculosis therapy and weekly injections of B_{12} and liver at her own request. She has rejected the idea of treatment with nitrogen mustard and possibly wisely so. A recent roentgenogram has shown no increase in size of the mass in her right lung and the impression of the radiologist at that time was that it was a malignant lesion. She has recently passed her seventy-ninth birthday and is planning to attend the next meeting of the American Medical Association.

[For further discussion of this interesting case see *J. A. M. A.* 170:137, May 2, 1959.—Ed.]

Cancer Symposia

• The annual scientific session of the American Cancer Society will be held October 26 and 27, 1959 at the Biltmore Hotel, New York City. The theme of this year's symposium will be "Evaluation of Early Diagnosis of Cancer." All members of the medical and dental professions, students, and those working in the allied sciences are invited. The scientific program is accepted by the American Academy of General Practice for 12 hours of credit in category II.

All inquiries should be addressed to: Director, Professional Education, American Cancer Society, Inc., 521 West 57th Street, New York 19, N. Y.

• The yearly clinical conference of the University of Texas, M. D. Anderson Hospital and Tumor Institute, will be held in Houston November 13 and 14. The theme of the conference will be "Tumors of the Head and Neck."

For information concerning the conference write to the editorial office, M. D. Anderson Hospital, Houston 25, Texas.

Cancer Etiology: New Prospective Epidemiological Study

E. Cuyler Hammond, Sc.D.

The probability of cancer occurring as a result of exposure to a carcinogenic agent apparently depends upon the potency of the agent, the degree of exposure, the duration of exposure and the susceptibilty of the individual. If a group of people are highly exposed to a powerful carcinogen over a period of many years, then the incidence of cancer in this group may be many times as great as the incidence of cancer in the general population. If such a group happens to be large, readily identifiable and subjected to some unusual exposure (e.g., chimney sweeps exposed to coal soot or radiologists exposed to x rays) then the unusually high incidence of cancer among them is very apt to be noticed. Once such an observation has been made, it is usually not very difficult to identify the responsible factor. This has led to the discovery of many different causes of cancer in human beings including ionizing radiation and a variety of organic and inorganic chemicals.

Except under such special circumstances as outlined above, an important cause of human cancer might well escape notice. For example, if the group under observation is small, an unusually high incidence of cancer might be attributed to chance. If the exposed group is scattered or not readily recognized as a group (e.g., people in all walks of life who have a certain habit in common), the incidence rate of cancer among them may not be recorded. If the carcinogenic agent is only moderately potent, then only highly susceptible individuals in the group might develop cancer and the incidence rate might not be so great as to attract attention.

Considering what is already known about causes of cancer in human beings, and considering the special circumstances which led to their discovery in each instance, there is reason to suspect that many cases of cancer result from exposure to environmental factors not yet identified as carcinogenic for human beings. In addition, animal experiments have demonstrated that certain agents (i.e., cocarcinogens) which are not in themselves carcinogenic can nevertheless increase the probability of the occurrence of cancer under specific sets of conditions. Furthermore, constitutional and inherited factors can influence susceptibility to cancer in experimental animals and the same may be true in human beings. Obviously, it would be useful to identify as many such factors as possible.

One approach to the problem is to learn as much as possible about the environment, habits and family history of a very large number of people and then ascertain the later incidence of cancer in relation to these factors. By starting with a population of several hundred thousand people in all walks of life, the number of individuals falling into specific exposure groups should be sufficient to yield reasonably reliable incidence rates.

This is the basis for a new prospective study about to be undertaken by the American Cancer Society. It may be described briefly as follows:

Several hundred counties in about twenty states will be selected as study areas. The selection will be made in such a way as to give a satisfactory geographic distribution. Cities of various sizes and types as well as rural areas will be included.

In each of these areas, volunteer workers of the American Cancer Society will be trained for the enrollment and trac-

From Statistical Research Section, American Cancer Society, Inc., New York, N. Y.

ing of subjects. The volunteers themselves will be so selected as to include all classes of society. Each volunteer will enroll about ten families (i.e., households) in which there is at least one person more than 45 years of age. All members of these families who are more than age 30 will be asked to fill out a questionnaire. In order to keep the information strictly confidential, each subject will put his questionnaire in a sealed envelope for transmittal to our office. The volunteer workers will not question the subjects and will not be permitted to see the filled out questionnaires.

The enrollment of subjects begins in October 1959 and should be completed within a short time. Once a year thereafter for the next six years, every subject will be traced. Causes of death will be ascertained from death certificates and additional medical information will be obtained on all cases where cancer is mentioned on the death certificate. In addition, once every two years the subjects will be requested to answer a brief questionnaire concerning illnesses occurring during the intervening period.

It is hoped that the analysis of the records will yield important clues as to a number of possible causes of cancer.

Two questionnaires are used, one for men and the other for women. These include sections on general characteristics (age, race, marital status, religion, etc.), family history, history of diseases, physical complaints, habits and exposures of various sorts, and a number of other items. On the form for women, special attention is given to questions relating to the breasts and female genital organs. On the form for men, special attention is given to occupation and occupational exposures. Questions relating to place of residence will be utilized to investigate the possible effects of air pollution. Information on twins in addition to information on family history and on husbands and wives should provide some data on possible inherited factors.

While the major purpose of the study is to investigate factors of possible etiologic significance, it is hoped that it will also yield information of value in relation to lay education. The subjects are asked detailed questions about "present physical complaints" and the answers will be analyzed in relation to cases of cancer diagnosed in the subsequent several months. Assuming, as is probable, that positive answers to certain of these questions are highly related to the presence of cancer, the data should be of value in persuading people with such complaints to see their doctors immediately. The aim, of course, is to reduce the factor of "patient delay" in the diagnosis of cancer.

Over a year has been spent in developing and pretesting the questionnaires. The evidence from this seems to indicate that subjects can answer most of the questions with a useful degree of accuracy. Some questions, particularly those on diet, present difficulty. For example, with a simple questionnaire, it does not appear to be possible to obtain accurate quantitative data on the consumption of various types of food. Nevertheless, it appears to be possible to identify those individuals whose dietary habits diverge greatly from the usual. Assuming that about 1,000,000 subjects are enrolled, at least 10,000 of them should fall into each of several extreme dietary groups. If diet is of importance in relation to cancer of some specific site, then a study of extreme groups of this size should at least yield a hint of the true association. The same might be said of a number of other factors under investigation in this study.

The procedures for the study were tested in field trials conducted in the fall of 1958 in five cities, Baltimore, Cleveland, Harrisburg, Nashville and Tampa. We were pleased to find that the volunteers were able to carry out their assignments very satisfactorily and that the subjects were most cooperative. Extremely few people who were asked to fill out questionnaires failed to do so and no serious objections were raised to any of the questions which are included in the final draft of the questionnaires.

We aim to enroll about 500,000 families with a total of about 1,000,000 individuals more than 30 years of age.

new developments in cancer

"Cancer Movement"

[Editorial, *New York Mirror*, July 13, 1959.]

The forthcoming report on cancer to be issued by Senator Humphrey's sub-committee will, of course, prove interesting. Cancer is the universal enemy of the human race—and we still know too little about it. Great progress has been made by research workers the world over. Such an organized research effort as the Sloan-Kettering Institute for Cancer Research in our own city is a monument to the enormous efforts of surgeons, chemists, biochemists and other scientists.

We spend billions of dollars on all sorts of prizes and premiums on such things. Why not set up a fund of one million gold dollars, which would be acceptable anywhere, to be given the first man or institution anywhere in the world who actually achieves a breakthrough in discovering the cause and cure for any form of cancer?

Perhaps some men of the medical profession might be squeamish about a money prize but they would welcome it to keep their work going.

Open Letter [To Editor, *New York Mirror* from Dr. Harold S. Diehl, Senior Vice President for Research and Medical Affairs and Deputy Executive Vice President, American Cancer Society, July 21, 1959.]

Your editorial of July 13, 1959, on the cancer movement suggests a prize of "one million gold dollars" for anyone who "achieves a breakthrough in discovering the cause and cure for any form of cancer." I submit that not only has such a breakthrough been attained, but that it has been made against the leading killer of men—lung cancer.

Throughout the scientific world it is widely accepted that smoking is the principal cause of lung cancer. This knowledge provides the means for preventing an estimated 75 to 85 per cent of all lung cancer. This year, 35,000 Americans will die of this preventable disease.

As Dr. Howard C. Taylor, Jr. expressed it in a report on tobacco and lung cancer at a committee meeting of the American Cancer Society's Board of Directors, "I am inclined to think that, so far as knowledge is concerned, we have had a breakthrough and we are unwilling to face its implications."

In terms of the large number of lives that can be saved from lung cancer as a result of this discovery, this achievement must be recognized as one of the major medical advances of all time. The real winner, of course, will be mankind when the "breakthrough" is fully exploited.

LUNG CANCER FACTS . . .

[*This is the second in the series on* Lung Cancer Facts *prepared by the Administrator for Research on Lung Cancer of the American Cancer Society.*—ED.]

The statement has frequently been made that the evidence linking cigarette smoking causally with lung cancer is entirely or "only" statistical. The purpose of this discussion is to examine experimental evidence to see whether these

assertions are correct.

Well over fifty papers have been published reporting studies of the effects of tobacco smoke or its condensates on biological systems. The experimental animals used include the mouse, rat, rabbit, dog, hamster, fowl and newt. In addition there are reports of pathologic changes in lungs of smokers and nonsmokers. Over ten modes of administration of tobacco tars have been used in five organ systems. Clearly, a thorough review of this literature can not be made in a few paragraphs.

Some of the salient facts, however, can be reviewed briefly. The gaseous phase of cigarette smoke contains water vapor, carbon dioxide, carbon monoxide and traces of ammonia and other gases. No one has seriously suggested that the gases lead to carcinogenesis. The particulate phase is the visible smoke consisting of minute heavy liquid particles which have condensed after pyrolysis of the tobacco, additives and cigarette paper. Each smoke particle is made up of thousands of organic compounds together with some that are inorganic. The organic compounds can be fractionated into acidic, basic and neutral components. While carcinogenic activity has been demonstrated in each of these fractions, twelve compounds known to be carcinogenic have been identified in the neutral fraction. They fall in the class of aromatic hydrocarbons; e.g., 1,2,5,6-dibenzanthracene and 3,4-benzpyrene. While the carcinogenicity of some of these compounds has been demonstrated only on skin or other nonpulmonary tissue, the two examples cited above have produced epidermoid lung cancers in mice and rats.

Thus at least two of the dozen compounds in tobacco smoke already known to have carcinogenic properties are specifically carcinogenic for the lung. An additional component, arsenic, once used extensively in insecticides by tobacco growers, is recognized as a carcinogen for man.

The facts cited above have led to the hypothesis that the aromatic hydrocarbons of cigarette smoke contain the carcinogenic agent(s) responsible for human lung cancer. The evidence, however, is insufficient to conclude that one or more of the cigarette tar carcinogens are the most important or even participate in the formation of human lung cancers.

It is estimated that the carcinogens known to be present in the neutral fraction of tobacco smoke represent only about 10 per cent of the carcinogenic activity for mouse skin. Little is known of the mutual inhibiting or augmenting properties of mixed carcinogens.

As important as the carcinogens may be, there is common agreement that noncarcinogenic substances must play a role either as cofactors with carcinogens of the smoke or with those inhaled from atmospheric pollutants. Pathologic changes have occurred in experimental animals exposed to inhalation of tobacco smoke but, so far, no invasive epidermoid lung cancers have been produced by this method.

It has been argued that the carcinogens of tobacco smoke are not present in sufficiently high concentration to be significant. Closer examination of the reports shows that the negative results might not be too surprising for other reasons: (1) To achieve one lung cancer in an experimental animal at the same rate as occurs in man would require 40 animals exposed to smoke. (2) Human smoking is oral; animals exposed to smoke breathe through the nose; they have highly developed sinus passages which filter the smoke. (3) The trachea of rodents used for inhalation studies is horizontal; man's is almost invariably vertical during smoking. Experimentally, cancers are produced more readily if the animals are placed vertically. In spite of these limitations, Leuchtenberger and others were able to obtain proliferative change in the epithelium consistent with "carcinoma in situ" and "similar to that described for human cigarette smokers by Auerbach, et al."

It must be concluded that there is considerable experimental evidence in addition to the statistical evidence contributing to the conclusion that cigarette smoking causes lung cancer. Some of the evidence not discussed here will be the subject of a subsequent discussion.

riety of mouse lymphoma cells in vivo and in vitro. Earlier, certain mouse lymphomas were inhibited in vivo by rabbit antisera plus normal guinea pig serum and guinea pig serum alone.

Shabad (Moscow): Inflammation does not stimulate carcinogenesis; carcinogens inhibit inflammatory reactions and distort their course. Benzoic extracts of cancer patients' livers induce tumors in mice. Saline extracts of human tumors have blastomatogenic activity.

Pullman (Paris): The K region -- the culpable atomic area of the carcinogenic molecule -- exists on the original carcinogen, not on its metabolites. The receptor molecule has no electron-seeking area.

Weiler (Pasadena): Rat hepatomas lack organ-specific mitochondrial and microsomal antigens. The kidney-specific antigen is lost in hamster kidney cancer; and the same kind of loss is undergone by normal kidney cells during their second generation of in vitro cultivation.

Ferrebee and others (Massachusetts General) have published a report in Blood, February, 1959, of a bone marrow bank being set up, using cadaver marrow as a source of viable cells. Intravenous administration of viable marrow cells has been shown in animals to bring about a repopulation of marrow spaces rendered aplastic by radiation, chemotherapy, or natural processes. It is the hope that a marrow bank can be put to similar use with human patients. The procedure for collecting and storing viable cadaver marrow involves removing vertebral bone marrow under sterile conditions within a few hours after death. The marrow cells are screened and suspended after centrifugation in an equal volume of a liquid medium consisting of 30 per cent glycerol and 70 per cent human serum and frozen at 80 degrees C. in plastic bags.

Hsu and Klatt (M. D. Anderson Hospital and Tumor Inst.) have found that hepatoma cells gradually change in chromosomal composition after long residence in vitro. The cell population shifts from a predominance of cells possessing either 39 (diploid number) or 78 (tetraploid number) chromosomes to an intermediate number, such as 67, 60 or 74, depending on the tumor strain. The original cells could be inoculated into young rats to produce tumors. After the chromosomal transformation, however, there was a marked decrease in transplantability, and if a tumor was produced, it would regress. In rats where such regression had oc-

curred, it was found that later they would reject any hepatoma grafts.

Lung Cancer Here and Abroad:

The Committee on Cancer Control of the Medical Society of the District of Columbia on July 21 passed a resolution to "support the American Cancer Society, District of Columbia Division, Inc. in its educational program as it relates to Junior and Senior High Schools, presenting the deleterious effects of smoking on good health." The Executive Board of the Medical Society of the District of Columbia approved the resolution.

[From Cancer: A Worldwide Menace; Some Facts and Figures on Its Occurrence in the United States and Abroad; Report to Hon. John L. McClellan, Chairman, Senate Committee on Government Operations from Hon. Hubert H. Humphrey, Chairman, Subcommittee on Reorganization and International Organizations, July 17, 1959.]

What is known about the occurrence of lung cancer in different countries?

Now the leading cause of cancer death for males in this country, cancer of the lung, pleura, and bronchi has been increasing rapidly both in incidence and mortality. Increases, in some instances of even greater magnitude, have been reported in many other countries. The level of mortality reached in England and Wales is especially striking. Prognosis for this type of cancer remains very poor, despite improvements in surgical techniques.

Epidemiological investigations of lung cancer have proved very fruitful. Excess risks have been shown to be associated particularly with cigarette smoking, urban residence, and certain occupations, such as processing of chromate ores. These have been demonstrated by data from a number of countries. Similarly, it has been shown that lung cancer incidence is greatest in the lowest socioeconomic groups in England and Wales, Denmark, and the United States.

Cancer research has three essential aims: the discovery of the cause or causes of cancer; the discovery of effective methods of diagnosis and treatment of cancer; and the discovery of methods for the prevention of cancer.

COMING MEDICAL MEETINGS

Date 1959	Meeting	City
Oct. 14-17	American College of Chest Physicians	Albuquerque
Oct. 15-17	Academy of Psychosomatic Medicine	Cleveland
Oct. 18-23	American School Health Association	Atlantic City
Oct. 19-23	American Public Health Association	Atlantic City
Oct. 21-22	American College of Preventive Medicine	Atlantic City
Oct. 23-25	American College of Cardiology	Philadelphia
Oct. 23-27	American Heart Association	Philadelphia
Oct. 26-27	American Cancer Society *Symposium on Evaluation of Early Diagnosis of Cancer*	New York City
Oct. 28-31	American Society of Tropical Medicine and Hygiene	Indianapolis
Nov. 2-4	Association of American Medical Colleges	Chicago
Nov. 2-5	Interstate Postgraduate Medical Association of North America	Chicago
Nov. 4-7	American Association of Blood Banks	Chicago
Nov. 6	Gastroenterology Research Group	Chicago
Nov. 6-7	Central Society for Clinical Research	Chicago
Nov. 7	Penrose Annual Cancer Seminar	Colorado Springs
Nov. 8-11	Association of Military Surgeons of the United States	Washington, D. C.
Nov. 12-14	Gerontological Society, Inc.	Detroit
Nov. 12-16	American Medical Women's Association	Hot Springs, Ark.
Nov. 13-14	Second Annual Symposium on Cinefluorography	Rochester, N. Y.
Nov. 15-20	Radiological Society of North America, Inc.	Chicago
Nov. 16-19	Southern Medical Association	Atlanta
Nov. 19-21	Inter-Society Cytology Council	Detroit
Nov. 19-21	Western Surgical Association	Colorado Springs
Nov. 22	Cancer Seminar, New Jersey Division, American Cancer Society, Inc.	Newark
Nov. 22-26	Puerto Rico Medical Association	Santurce, P. R.
Dec. 11-12	New York Heart Association	New York City
1960		
Jan. 9	Northwest Society for Clinical Research	Seattle
Jan. 21-23	American College of Surgeons	Louisville, Ky.
Jan. 28-30	Western Association of Physicians	Carmel, Calif.
Jan. 28-30	Western Society for Clinical Research	Carmel-by-the-Sea, Calif.
Feb. 3-6	American College of Radiology	New Orleans
Feb. 10-12	American Academy of Occupational Medicine	Williamsburg, Va.
Feb. 11-13	Society of University Surgeons	Minneapolis
Feb. 18-20	Central Surgical Association	Chicago
Feb. 21-24	California Medical Association	Los Angeles
Feb. 25-27	M. D. Anderson Symposium on Fundamental Cancer Research	Houston
Feb. 29-Mar. 3	American College of Surgeons	Boston

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